New Delhi Metallo-β-Lactamase and Multidrug Resistance: A Global SOS?

Robert A. Bonomo
Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio

(See the Brief Report by Sidjabat et al, on pages 481–484.)

A case report of a multidrug-resistant (MDR) infection with a strain of *Klebsiella pneumoniae* carrying a novel metallo-β-lactamase (MBL), the New Delhi MBL (NDM-1), appears in this issue of *Clinical Infectious Diseases* [1]. Sidjabat and colleagues detail the presentation and susceptibility profile and give us a brief molecular characterization of an isolate of *K. pneumoniae* carrying blaNDM-1 that was recovered from an 87-year-old Australian woman of Indian origin with a urinary tract infection. What is the significance of these findings? Is this really a “superbug”?

In gram-negative bacteria, 2 types of β-lactamases are responsible for resistance to carbapenems: those that use serine as the active site amino acid to inactivate the carbapenem (“serine carbapenemases”), and those that use a Zn$^{2+}$ ion (“metallo β-lactamases” or MBLs) [2]. In the 1980s and 1990s, carbapenemases were considered the “last resort antibiotics” used primarily against extended-spectrum β-lactamase (ESBL)– or AmpC-producing gram-negative bacteria. At that time, only a few β-lactamases could inactivate carbapenems, and these were limited to rare strains of *Enterobacter cloacae* possessing serine carbapenemases called NMC-A (Non Metallo Carbenemase) and IMI-1 (Imipenemase-I), Sme-1 (*Serratia marcescens*), MBLs Bcl and BcII of *Bacillus cereus*, the MBL L1 of *Stenotrophomonas maltophilia*, and CcrA of *Bacteroides fragilis* (another MBL) [3]. In a very short time, serine carbapenemases and MBLs became more frequent. MBLs are now widespread and found in Europe, Asia, Australia, Canada, and South and North America [4–8].

Presently, physicians practicing in tertiary care referral centers, long-term acute care hospitals, and nursing homes in large urban areas of the United States are acutely aware of carbapenem-resistant gram-negative bacteria carrying the gene for KPC (*Klebsiella pneumoniae* carbapenemase, blaKPC) [9–12]. In the United States, KPC-producing gram-negative bacteria (usually found in *Klebsiella* species, *Escherichia coli*, *Proteus* species, *Enterobacter* species and others) raised significant concern, because mortality rates among patients infected with these bacteria are high, especially in long-term care facilities [11]. Moreover, detection of this resistance determinant in the clinical microbiology laboratory is still challenging [13]. The most widespread MBL in the world (thus far) is VIM-2 (isolated first from a patient in Verona, Italy—hence the name *Verona Imipenemase*) [2, 6, 14, 15]. Up until now, MBLs have been rarely reported in the United States, save for descriptions of VIM-type β-lactamases found in Texas and Illinois [14, 16]. Many believe that we might never see this problem in the United States. Will NDM-1 be the MBL that changes this? How will we readily distinguish between carbapenem-resistant KPC and NDM-1–producing gram-negative bacteria by phenotypic methods?

NDM-1 attracts significant attention because the gene encoding this MBL is located in a very mobile genetic element and the pattern of spread is proving to be more complex and, apparently, more unpredictable than the gene encoding KPC [17, 18]. In fact, the number of patients infected or colonized with bacteria possessing blaNDM-1 is growing. The gene has moved from India and Pakistan to the United Kingdom, the United States, Kenya, Japan, Canada, Belgium, the Netherlands, Taiwan, Singapore, the Sultanate of Oman, and Australia [19–25]. A review of the original description of blaNDM-1 by Yong et al [17] sets the background for the
importance of this dissemination. The notable points established are:

1. bla<sub>NDM-1</sub> is found on plasmids of different sizes. This is important, because there are genetic signatures flanking bla<sub>NDM-1</sub> that have implications for mobility and for pathogenesis (bla<sub>NDM-1</sub> was also near a pathogenicity island).

2. The mobility of the genetic element containing bla<sub>NDM-1</sub> is significant. Therefore, we might anticipate finding this gene or gene cassette in other gram-negative bacteria from the same patient. Moreover, the isolates with bla<sub>NDM-1</sub> were also colonizers. In the article by Yong et al [17], there were 2 isolates containing bla<sub>NDM-1</sub>: a K. pneumoniae isolate (from a urine specimen) and an E. coli isolate (isolated from a fecal swab). Isolates containing bla<sub>NDM-1</sub> can be carried without the presence of disease, making screening difficult.

3. The resistance determinants in this K. pneumoniae were numerous, including 2 chromosomal β-lactamases (bla<sub>CMY</sub> and bla<sub>DHA</sub>), chloroamphenicol and aminoglycoside resistance genes. There was also a new erythromycin-resistance gene found. Like the case in this issue of the journal, the genetic basis of the MDR phenotype is notable. These genes travel in “bad company”. A recent report by Poirel et al [20] of a strain of Citrobacter freundii carrying bla<sub>NDM-1</sub> also possessed 9 different β-lactamase genes.

Therefore, this case report and other studies describing the emergence of NDM-1 are an important warning and reminder [26]. The recent Morbidity and Mortality Weekly Report released in the month of May alerts us to the presence of NDM-1, even in the United States [25]. It may only be a matter of time until US hospitals face a large outbreak.

We should keep in mind that the report of the large outbreak in the United Kingdom, India, and Pakistan was a surveillance study [26]; the problem was noted only after the spread of NDM-1 occurred. People travel very frequently and populations harboring the NDM-1 resistance determinant are sure to cause concern here. Therefore, the MBL NDM-1 is a wake-up call—an SOS! The world now has another threatening pathogen added to the list (see www.idsociety.org: methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, ESBLs, etc … and NDM-1?) to remind us that we do not have enough resources dedicated to preventing or treating infections with MDR pathogens.

How do we effectively deal with this? In general, bacteria containing NDM-1 β-lactamase seem to test susceptible to colistin or tigecycline, but experience dictates that this will be short lived, because colistin-resistant NDM-1-producing isolates have also been found [1]. Do we have new β-lactams in the pipeline to treat pathogens possessing NDM-1? Maybe combinations using aztreonam or similar monobactams that are resistant to hydrolysis eg, by MBLs can offer hope [27]? However, one needs to keep in mind that many of these NDM-bearing strains also have AmpC cephalosporinases and/or ESBLs that can hydrolyze aztreonam, so an inhibitor of these will need to be added (NXL104, although it has not yet been approved). Other drugs that escape resistance by these strains need to be tested in clinical trials. Fosfomycin is effective against KPC-producing K. pneumoniae, but will resistance emerge quickly [28]? Certain NDM-1-bearing strains also possess 16S rRNA methylases, making all aminoglycosides ineffective, including the neoglycoside ACHN-490 [29, 30].

What is the solution? We need a national and international monitoring system. We submit that our current programs of surveillance and resistance tracking in the United States be linked strongly with international agencies and further developed and organized to monitor these threats locally and globally. In my view, MDR infection, whether due to MBLs such as NDM-1 or KPCs, is a worldwide health problem that is slowly becoming as important as human immunodeficiency virus infection, malaria, and extremely drug-resistant tuberculosis. Nations need to organize and dedicate containment and research efforts to develop high-impact programs that find better ways to detect, monitor, report, and analyze health threats such as this. A recent program was developed in France that screens for MDR bacteria producing carbapenemases in patients transferred from foreign hospitals [20]. Is this what the United States also needs [31]? NDM-1 is only a singular warning in an already escalating and frightening problem. Given our current approach in the United States to KPCs and MDR infections and the level of commitment to infection control and antibiotic resistance research, one worries that little will be done unless it has to be done—or when it is too late. The genetic prowess already exhibited by the constructs harboring bla<sub>NDM-1</sub> is remarkable; one can only imagine the scope of territory and human lives potentially at risk. With the help of national and international organization, we need the implementation of screening coupled to rapid diagnostic platforms using state-of-the-art molecular diagnostic probes that can be done easily and accurately. The presence of NDM-1 is telling us the landscape in infectious diseases is approaching a tipping point. We need to respond to this distress call now.

Acknowledgments

I give special thanks to Ms Kristine M. Hujer and Ms. Andrea M. Hujer for editorial assistance. Financial support. R.A.B. is supported by the Merit Review Program of the Department of Veteran Affairs and by grants from the NIH. He is a consultant for Pfizer.

Potential conflict of interest. All authors: no conflicts.

References

1. Sidjabat H, Nimmo GR, Walsh TR, et al. Carbapenem resistance in Klebsiella...
pneumoniae due to the New Delhi metallo-β-lactamase (NDM) clinical infectious diseases 2010.


