Does broad-spectrum β-lactam resistance due to NDM-1 herald the end of the antibiotic era for treatment of infections caused by Gram-negative bacteria?

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The NDM-1 gene, first identified in Sweden in 2008 in Klebsiella pneumoniae from a patient hospitalized in New Delhi, encodes a metallo-β-lactamase that inactivates all β-lactams except aztreonam. This blaNDM-1 gene has been identified in hospital-acquired bacterial species, such as K. pneumoniae, but also in the typical community-acquired species, Escherichia coli. This gene has been identified in strains that possess other resistance mechanisms contributing to their multidrug resistance patterns. It has been recently extensively reported from the UK, India and Pakistan and, albeit to a lesser extent, from a number of other countries worldwide. In most of the cases a link with the Indian subcontinent has also been established. To stem the onslaught of NDM producers, early identification of cases of NDM-related infections and prevention of their spread by implementing screening, hygiene measures and the isolation of carriers is needed.

Keywords: metallo-β-lactamases, carbapenemases, Enterobacteriaceae, India, Pakistan

Introduction

NDM-1 (where NDM stands for New Delhi metallo-β-lactamase) is a broad-spectrum β-lactamase (carbapenemase) that is able to inactivate all β-lactams except aztreonam, as is typical of metallo-β-lactamases (e.g. IMP and VIM).1 The first case of an NDM-1 producer was from a Swedish patient previously hospitalized in New Delhi, encodes a metallo-β-lactamase that inactivates all β-lactams except aztreonam. This blaNDM-1 gene has been identified in hospital-acquired bacterial species, such as K. pneumoniae, but also in the typical community-acquired species, Escherichia coli. This gene has been identified in strains that possess other resistance mechanisms contributing to their multidrug resistance patterns. It has been recently extensively reported from the UK, India and Pakistan and, albeit to a lesser extent, from a number of other countries worldwide. In most of the cases a link with the Indian subcontinent has also been established. To stem the onslaught of NDM producers, early identification of cases of NDM-related infections and prevention of their spread by implementing screening, hygiene measures and the isolation of carriers is needed.

Spread of NDM-1 producers

Although KPC, OXA-48, VIM and IMP producers are currently the most widespread types of carbapenemase in Enterobacteriaceae, NDM-1 producers are likely to become highly prevalent. As of 1 November 2010, the number of identified NDM-positive cases remained limited mostly, but not exclusively, to nosocomial infections. Around 70 cases have been identified in the UK, 150 in India and Pakistan,3 3 in Australia, 2 in Austria,6 only to colistin and tigecycline.3 These resistance patterns reflect our first concern, which is the end of our current pharmacopeia. Carbapenemases of various types (IMP, VIM, KPC and OXA-48) have been previously identified mostly in K. pneumoniae, which is a typical nosocomial pathogen.1,4,5 Carbapenemases have rarely been reported from E. coli, which is typically widespread in the environment and in water and which is an important bacterium of the human intestinal flora, easily transferred by hand, water or an inanimate environment from person to person. E. coli is the cause of many community-acquired infections, such as diarrhea and urinary tract infections. Therefore, identification of a significant number of NDM-1 producers in E. coli is an additional source of concern as it suggests that the resistance is being disseminated in the environment as well as in the hospital.
2 in Belgium,7 4 in Canada,8,9 3 in China, 2 in Germany,10,11 1 in Hong Kong,12 1 in Israel, 1 in Japan, 2 in the Netherlands,13 2 in Norway,14 1 in Singapore,15 1 in Sweden,2 1 in Taiwan16 and 3 in the USA.17,18 We have recently identified additional cases in Australia (1),19 France (2 out of the 4 known cases),20,21 Kenya (7)22 and the Sultanate of Oman (2)23 (Figure 1). Several fatal cases of infection due to NDM-1 producers have been reported from a number of countries including the UK, India and Belgium. In most of the cases, patients had been hospitalized in India, Pakistan or Bangladesh, were of South Asian origin or had spent some time in that part of the world. It is therefore compelling that the Indian subcontinent is currently the main reservoir of NDM-1 producers. The identification of that reservoir at a national level is critical since >1.3 billion people are living on the Indian subcontinent. Overcrowding coupled with poor hygiene, difficulty in obtaining potable water, poor sanitation, sale of non-prescribed antibiotics (self-medication) and weak hospital antibiotic policies may be contributing factors for selecting and facilitating the spread of NDM-1 producers. However, it is important to emphasize that recent studies identified NDM-1-producing isolates from patients originating from different countries located in the Balkans region, such as Montenegro,7 Serbia13 and Kosovo,6 and the Middle East (Oman23 and Iraq24). Those regions could therefore constitute secondary reservoirs for NDM-1 producers.

The Indian subcontinent, like many other areas in the world, has witnessed a rising trend of E. coli producing extended-spectrum β-lactamases (ESBLs) since the beginning of the 2000s.25 Those ESBLs, which are mostly of the CTX-M-15 type, confer resistance to all β-lactams except cephemycins and carbapenems.26 In fact, we identified the first worldwide reported case of a CTX-M-15 producer in 2000 from India25 and subsequent to that study have shown CTX-M-15 producers in India from 1998.27,28 India is now one of the countries with an extremely high rate of CTX-M producers, comprising >70% of E. coli according to a 2007 survey.28 Spread of ESBLs in India/Pakistan/Bangladesh may be an important driving force for usage of carbapenems for treating any infections including the less complicated urinary tract infections, and consequently a driving force for selection of NDM-1 producers. NDM-1 producers possess mostly ESBLs of the CTX-M-15 type, but also express broad-spectrum aminoglycoside resistance enzymes, such as acetyltransferases and methylases, and topoisomerase mutations leading to a high level of resistance to fluoroquinolones, resulting in multidrug resistance patterns.28

It is difficult to predict the rate of spread of the gene encoding NDM-1 in the faecal flora of patients in the Indian subcontinent. Exchanges of the blaNDM-1 gene between unrelated bacterial isolates and species has been identified already in Enterobacteriaceae and Acinetobacter baumannii.29,30 An Indian report indicates rapid spread of carbapenem-resistant enterobacterial species in a hospital in Mumbai.31 There is now an urgent need to evaluate the spread of NDM-1 among hospital-acquired and community-acquired pathogens in the Indian subcontinent for safe recommendation of voluntary hospitalization in these hospitals (450000–600000 persons a year), as in other parts of the world where enterobacterial producers of other types of carbapenemases are widespread, such as in Greece and in the eastern part of the USA.4 In addition, the carrier state of NDM-1 producers has to be quickly estimated to predict its generic spread. It is also noteworthy that an estimated 5 million tourists visited India/Pakistan in 2008 while an

![Figure 1. Worldwide distribution of identified cases of NDM-1 producers, 1 December 2010.](image-url)
estimated 10 million nationals left those countries in the same year (http://tourismindia.com). It is possible that the dissemination of the \( \text{bla}_{\text{NDM-1}} \) gene will mirror the spread of the \( \text{bla}_{\text{CTX-M-15}} \) gene, and that thousands of South Asian people may be carriers of multidrug- or pan-resistant \( E. \text{coli} \) isolates expressing the \( \text{bla}_{\text{NDM-1}} \) gene in their faecal flora. Those \( E. \text{coli} \) isolates may be responsible for transmissible infections (mostly community-acquired diarrhoea and urinary tract infections) and the reservoir of transmission of the \( \text{bla}_{\text{NDM-1}} \) gene to other bacterial species, such as \( K. \text{pneumoniae} \). That latter species has been proved to be a powerful pathogen for dissemination of ESBL genes as a source of multidrug resistance in hospital-acquired infections. Thus, spread of the \( \text{bla}_{\text{NDM-1}} \) gene in \( K. \text{pneumoniae} \) may be the source of many outbreaks of pan-resistant bacteria.

Considering the rapid population exchanges at the beginning of the 21st century, uncontrolled NDM-1-related resistance may be expected to be identified not only in India, Pakistan and Bangladesh, but also in countries with important population exchanges with the Indian subcontinent. Those countries with an important Indian/Pakistani diaspora (20 million in 110 countries) are mostly the UK, South Africa, the Gulf states, Australia, Canada and the USA. As observed recently in the UK, transfer of NDM-1 producers is likely to be first seen in the hospital setting related to transfer of patients previously hospitalized in the Indian subcontinent.

What shall be done?

In fact, it has been shown for many years that hospitalized patients are the main carriers of multidrug-resistant isolates. This perspective explains the French Health Authority decision taken in September 2010 to screen all patients hospitalized abroad for multidrug-resistant bacteria on the day of their admission to any French hospital, i.e. in the carriage state. We fully supported this approach, now also under discussion in several other countries, as it should enhance early detection of NDM-1 producers in infections, which, in turn, may prevent further spread of these multidrug-resistant bacteria. Use of techniques developed for detection of NDM-1 producers should be promoted worldwide.12

The possible spread of NDM-1 producers reinforces the urgent need to develop novel anti-Gram-negative molecules and the implementation of a worldwide network of sentinel laboratories for antibiotic resistance surveillance, as seen for surveillance of other diseases such as influenza. Any broad-spectrum resistance trait emerging in \( E. \text{coli} \) is of primary importance since it remains the most important human pathogen leading to a significant degree of mortality when left without efficient antibiotic therapy.

In 2000, the WHO produced their comprehensive recommendations for curbing antibiotic resistance.13 These recommendations include national surveillance programmes, rigorous infection control policies, banning of non-prescribed antibiotics, prudent antibiotic usage in hospitals and increased international collaboration. Unfortunately, not only have some countries failed to implement such recommendations, but they have barely been acknowledged. The spread of NDM-1 constitutes a study in real time of how resistance can become global. Critically, it warns us that antibiotic resistance can become a global problem that requires bold and decisive global action. It is essential that such recommendations are no longer ignored but fully implemented in a transparent and accountable manner.

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Transparency declarations

None to declare.

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