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News and Perspective

A Continuous Challenge from Gram-negative Bacteria: More Carbapenemases

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A new type of carbapenemase, New Delhi metallo-β-lactamase (NDM)-1, has been recently identified in *Enterobacteriacae* isolates. Multidrug resistant NDM-1 pathogens spread quickly and caused human infections in the community and hospitals in many countries. This finding has attracted worldwide attentions.[1] The $bla_{\text{NDM-1}}$ gene encodes an enzyme, which confers resistance to carbapenems and other β-lactams. The $bla_{\text{NDM-1}}$ gene harbors in *Enterobacteriacae*, mainly *Klebsiella pneumoniae* and *Escherichia coli*, which can cause community-onset or healthcare-associated infections. The first case of NDM-1 infection was found in a Swedish patient of India origin, who has been admitted to a hospital in New Delhi.[1] Besides, Kumarasamy et al demonstrated the outbreak of NDM-1-producing bacteria in India, Pakistan and United Kingdom.[2] They found that $bla_{\text{NDM-1}}$ gene was detected in 1–13% of carbapenem-resistant *Enterobacteriacae* strains in India, and NDM-1-producing isolates predominated in 44% of the carbapenemase-producing *Enterobacteriacae* in the United Kingdom since 2008. Moreover, many patients in the United Kingdom with NDM-1-producing Gram-negative bacilli had traveled to India or Pakistan within the same year.[2] Similar infections have been observed in the United States, Candida, Australia and the Netherlands,[3,4] suggesting a possibility of global spread.

The NDM-1 carbapenemase poses little genetic identity to other metallo-β-lactamases, but shares 32.4% of identity with VIM-1/VIM-2. NDM-1 can hydrolyze all β-lactams except aztreonam,[1] but universal resistance to aztreonam in clinical NDM-1-producing isolates suggested that the possibility of concurrent presence of additional β-lactamses, which had been identified as AmpC and extended-spectrum β-lactamases (ESBLs) enzymes.[2] These findings are not surprising because recent studies demonstrated the prevalence rate of ESBLs in *Enterobacteriacae* reaches 70–90% in India.[5] Moreover, the NDM-1-producing pathogen is highly resistant to other antibiotics, such as fluoroquinolones and aminoglycosides, which were clinically used for Gram-negative infections.[2] A good news is that these isolates remain susceptible to tigecycline (56–67%) or colistin (89–100%).[2] However, low concentration of tigecycline in serum with presently recommended dosages precluded its use for bacteremia, and colistin therapy was often hesitated due to its nephrotoxicity in critically ill patients. So far, there is no susceptibility information of fosfomycin for NDM-1-producing pathogens, but a worrisome fact is that fosfomycin susceptibility is lower in ESBL- or metallo-β-lactamase- producing *Enterobacteriacae* than those

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isolates without indicated β-lactamases.[6] Nevertheless, it is predictable that the clinically available drugs for infections caused by NDM-1-producing pathogen will be very limited, and currently few antibiotics with significant antibacterial activity against Gram-negative bacteria are under development in pharmaceutical industry.[7]

A recent study highlighted that NDM-1-producing strains had a ready access of transferring its resistant genes to other *Enterobacteriacae* species through transconjugation.[1,2] A molecular epidemiological survey revealed that some isolates with NDM-1 in India were clonally related while the others were clonally diverse.[2] Therefore, it is highly possible that NDM-1-producing pathogens can be globally spread. To make it worse, the global explosion of CTX-M-type ESBL in *Enterobacteriacae* makes the therapeutic choice shifting towards carbapenems. The selective pressure for the emergence of carbapenemase-producers would grow up consequently. The typical scenario for the former was the emergence of a novel carbapenemase, *K. pneumoniae* carbapenemase (KPC), which spread worldwide and caused hospital-associated infections in many countries.[8–10] Although KPC and NDM-1 β-lactamases share a similar phenotype of carbapenems resistance, NDM-1-producing strains,[11] but not KPC-producing strains,[12] could be recognized by the current screening methods of MBL production, such as modified Hodge test, imipenem-EDTA double-disc synergy tests, or metallo-β-lactamase E-test (AB bioMerieux, Solna, Sweden).[1] Comparisons of epidemiological and microbiological characters of KPC and NDM-1-producing bacteria are summarized in the Table.

The variation of medical services and expenditure between countries would have an impact on the epidemiology of infectious diseases. For example, it is not uncommon

Table. Summary of microbiological and epidemiological features of two carbapenemases, NDM-1 and KPC

Characteristics	NDM-1	KPC
Year of identification	2009	2001
Endemic areas	India, Pakistan & United Kingdom	Worldwide
Clone spread	Yes (some are diverse clones)	Yes
Source of infection	Community and hospital	Hospital
Bacteria species	Mainly *K. pneumoniae* or *E. coli*; *Enterobacter* spp., *Citrobacter freundii, Morganella morganii, Providencia* spp.	Predominately *K. pneumoniae*
Horizontal transmission to other species	Possible	Rare
Drug resistance[a]	Highly resistant	Highly resistant
Carbapenem resistance	High	High
Susceptibility to candidate antibiotics		
Colistin	Susceptible	Susceptible
Tigecycline	Intermediate	Resistant
Gentamicin	Resistant	Susceptible
Fosfomycin	Unknown	Intermediate
Screening test	MBL production positive (Modified Hodge test, imipenem-EDTA synergistic test, MBL E-test)	MBL production negative; imipenem-boronic acid disk synergy test positive
Confirmation test	PCR detection of bla_{NDM-1} gene	PCR detection of bla_{KPC} gene
Infection control in hospitals	Contact isolation	Contact isolation

[a]Strains with NDM-1 or KPC are resistant to nearly all β-lactams. NDM=New Delhi metallo-β-lactamase; KPC=*Klebsiella pneumoniae* carbapenemase; MBL=metallo-β-lactamase; EDTA=ethylenediaminetetraacetic acid; PCR=polymerase chain reaction.

for people to access medical care in different countries for economic reason. The so-called "medical tourism" would facilitate the spread of multidrug-resistant bacteria between continents. It is evident that many patients with infections due to NDM-1-producing bacteria had received surgeries in India.[4] Therefore, some experts advocate that it merits regular screening of multidrug-resistant pathogens, especially for those with a history of medical care in endemic countries.[4]

Physicians worldwide are facing the growing challenge of carbapenem-resistant Gram-negative bacteria. Clinicians should be alert of the possibility of NDM-1-producing *Enterobacteriacae* infection in patients ever having medical care in endemic areas. Optimal antimicrobial therapy warrants further *in vitro* and clinical studies. Patients with infection or colonization due to NDM-1-producing pathogens in the hospital should be placed in contact isolation.[13] As for routine practices in microbiological laboratories, carbapenem resistance and carbapenemase production conferred by $bla_{\text{NDM-1}}$ can be detected by phenotypic methods as recommended by the Clinical and Laboratory Standards Institute.[14] Strains obtained from patients receiving medical care in endemic areas, and with carbapenem resistance and metallo-β-lactamase production, should be submitted for NDM-1 screening. Moreover, the emergence of multidrug-resistant bacteria highlights the needs for international collaboration with a worldwide, multicenter surveillance for the emergence of those superbugs.

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