

New Delhi Metallo- β -lactamase among clinical isolates in Nepal

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ABSTRACT

Background: Incidence and drug resistance of the isolates producing New Delhi Metallo- β -lactamase (NDM) has been increasing throughout the world. Nepal is located between India and China from where abundant reports of NDM detection has been reported in recent days but in Nepal, very few studies are there. Hence this review was done to know the status of NDM in Nepal and its various characteristics. **Method:** Research articles reporting NDM producing isolates from Nepal published before June 2018 were searched using various scientific databases using specific keywords and required data were extracted. **Result:** According to the reviewed articles, NDM was prevalent in *E.coli*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Providencia* and other members of Enterobacteriaceae in Nepal. Seven variants of this gene were reported including NDM-1, NDM-3, NDM-4, NDM-7, NDM-8, NDM-12, and NDM-13. These pathogens were not susceptible to almost all routine drugs due to co-existence of NDM gene with the wide variety of other drug resistance genes like Carbapenemases, ESBL, 16S rRNA methylases etc. Most of them were sensitive only to colistin, tigecycline, and fosfomycin. Some of these isolates were extremely drug-resistant as well as resistant to colistin, one of the last resort drugs. **Conclusion:** High drug resistance of these isolates and their distribution among major human bacterial

pathogens necessitates the prompt surveillance of these pathogens throughout the country, monitoring their resistant patterns, judicious antibiotic use, screening of these isolates from clinical, food, and environmental isolates and development of appropriate control measures.

Keywords: Clinical isolates, Nepal, New Delhi Metallo- β -lactamase

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INTRODUCTION

NDM is a class B Metallo- β -lactamase, which is disseminated worldwide in different bacterial isolates after its first appearance in 2009 [1]. These isolates are predominant in the Indian subcontinent as they have been reported from India, Pakistan, and Bangladesh [2]. Isolates carrying NDM are regarded as superbugs due to their high drug resistance, except few last line antibiotics like colistin and tigecycline and dissemination of such isolates pose significant threat to global public health [3]. NDM has been detected among a variety of antibiotic-resistant gram-negative pathogens isolated from health care and community setting of Pakistan and India, as well from more than 15 countries of the globe [4]. NDM producing bacterial isolates are equipped with minimum one copy of partial or full ISAb₁₂₅ gene which acts as

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a powerful promoter of this gene and NDM producing members of Enterobacteriaceae are related with travel to South Asia in many cases [5]. This Metallo- β -lactamase is a great concern as the gene for this enzyme is placed in the highly mobile genetic segment. In addition to this, it has a highly complex and possibly uncertain mode of dissemination than *Klebsiella pneumoniae* carbapenemase [6]. There is a simultaneous spread of NDM and emergence of its variants as indicated by reports of 10 NDM variants already. Some NDM variants like NDM-4 and NDM-5 pose higher carbapenemase activity compared to NDM-1 wild type, leading to increased resistance to β -lactam drugs and hence there is a demand of surveillance of NDM as well as its variants to know the epidemic and β -lactam resistance by these isolates [7]. Zinc ions are necessary for NDM to breakdown β -lactam drugs, as a result, its activity can be impeded by metal chelators i.e EDTA while its activity is not hindered by all known inhibitors of β -lactamase i.e tazobactam, sulbactam and clavulanate [8]. In this decade, NDM gene has also been detected from Nepal [9–20].

Study of drug-resistance genes and their mechanism among clinical isolates are very rare in Nepal. Hence, the actual prevalence of ESBL, carbapenemase and other resistance genes among pathogens are not well known. Among the resistance genes, NDM is one of the significant genes as its high level of resistance and mode of rapid spread. The data regarding the status of NDM in Nepal is not available till now. Hence, this review was carried out to access the current scenario of NDM in Nepal and its various aspects. To our knowledge, it is the first review article regarding this highly notorious gene in Nepal.

MATERIALS AND METHODS

Literature search

A systematic literature search was carried out for New Delhi Metallo- β -lactamase in Nepal from various electronic databases (Medline via PubMed and Embase) published till May 2018. Original research articles available in English indicating NDM detection using molecular methods from Nepal were only included in this study (Figure 1). Following keywords were used during literature search in title and abstract of the articles: NDM, NDM variants, Nepal, gram-negative isolates, Multi-drug resistant, incidence.

Inclusion and exclusion criteria

Research articles fulfilling following criteria in abstract and/ or text were included in the study; i) detected NDM gene from gram-negative pathogens isolated in Nepal, ii) used valid molecular methods for the NDM gene detection, iii) provided various characteristics of NDM producers like isolate producing NDM, duration of study, NDM variants, study site and antibiotic susceptibility profile. Similarly, the exclusion criteria were; i) lacked

the valid molecular method of NDM detection, ii) lacked various characteristics of NDM producers, iii) review articles, iv) duplicate articles of the same study, v) articles not in English language, vi) meta-analysis, and vii) abstract only articles.

Data extraction

Following variables were extracted from the selected studies: isolate producing NDM, source specimen of the isolates, duration of a study, the presence of other resistant gene, NDM variants, antibiotic susceptibility profile and study site. Two reviewers independently reviewed the selected articles fairly and discussions were made to settle discrepancies between two reviewers.

RESULT

NDM producers were detected in members of Enterobacteriaceae (mainly *E.coli* and *Klebsiella*) and non-fermenting gram-negative isolates. These isolates have been reported from various clinical specimens after 2012 in Nepal. Most of the isolates were highly drug-resistant as they were resistant to almost all members of antibiotics related to different classes. Some of these isolates also produced various other resistant determinants leading to increased resistance to nearly all tested antibiotics as indicated by increased MIC values [11, 12]. They were also not affected by a combination of beta-lactam and beta-lactamase inhibitors like ampicillin-tazobactam piperacillin-tazobactam and ampicillin-sulbactam (Table 1).

If we compare the distribution and other characteristics of NDM positive clinical isolates between Nepal and India, very similar results can be seen. In India, NDM has been reported in *Acinetobacter baumannii* [21], *E.coli*, *Klebsiella spp*, *Enterobacter spp* [22, 23], *E.coli*, *Klebsiella spp*, *Citrobacter spp*, *Proteus spp*, *Serratia spp* and *Acinetobacter spp* [24], *Pseudomonas aeruginosa* [25, 26], *Klebsiella pneumoniae* [27], *E.coli* [28] and *E.coli*, and *Klebsiella pneumoniae* [29]. Most common variants of NDM were NDM-1 [21–25] while other variants like NDM-4, NDM-5, and NDM-7 were also detected [28]. Indian NDM bearing isolates were also very resistant to routine antibiotics including imipenem, meropenem, gentamicin, amikacin, netilmicin, and tobramycin [21], ertapenem, aztreonam, and cefepime [25], ceftazidime, cefotaxime, ciprofloxacin, and tigecycline [27], ampicillin, ampicillin-sulbactam, cephalothin, cefoperazone, cefazolin, and clarithromycin [28] and piperacillin-tazobactam, cefpirome, and minocycline [29]. Such high drug resistance was attributed due to co-production of NDM genes with blaOXA [21–23], blaKPC-2 [25], blaVIM and blaIMP [26], blaKPC-2, blaSHV-12, blaCTX-M-15, blaTEM-1, rmtB and blaOXA-1 [27] and blaCTX-M-15, tem, aac6', qnrB, qnrS, tetA, tetC, sul1, sul2, dfr and strA [28] genes. These isolates were sensitive, only to colistin or tigecycline or their combination [21, 27–29].

Table 1: Characteristics of NDM positive isolates detected from Nepal

Isolate	specimen	Duration of study	NDM variant	Other resistance factors	Sensitive to	Resistant to	Study site	Ref
<i>E. coli</i>	Pus	2012	NDM-8	-	Fosfomycin, colistin, tigecycline	Ampicillin, ampicillin-tazobactam, Aztreonam, cefepime, Cefotaxime, Cefoxitin, Ceftazidime, Cephadrine, Imipenem, Meropenem, Penicillin G, piperacillin, piperacillin-tazobactam, ticarcillin, Ticarcillin-clavulanic acid, arbekacin, amikacin, gentamicin	TUTH*	9
Acinetobacter	-	2014-15	NDM-1	bla OXA-23, bla OXA-51	colistin	ceftazidime, imipenem		10
Providencia rettgeri	Pus and sputum	2012	NDM-1	bla OXA-10, bla VEB-1, bla TEM-1, bla ADC-67, armA, aadA1, aadA2	-	Piperacillin, piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, doripenem, aztreonem, amikacin, genotamicin, ciprofloxacin, colistin, fosfomycin	TUTH*	11
<i>E. coli</i>	Urine	2013	NDM-12	-	Fosfomycin, colistin, tigecycline	Ampicillin, Ampicillin-sulbactam, Aztreonam, Cefepime, Cefotaxime, Cefoxitin, Ceftazidime, Ceftriaxone, Doripenem, meropenem, imipenem, amikacin, arbekacin, ciprofloxacin, gentamicin, kanamycin, tobramycin, levofloxacin	TUTH*	12
<i>P. aeruginosa</i>	-	2012-13	NDM-1	VIM-2, PDC-35, RmtB4, AACA7, AAC5b	colistin	Imipenem, meropenem, aztreonam, ceftazidime, amikacin, arbekacin, ciprofloxacin	TUTH*	13
<i>E. coli</i> , Acinetobacter, Pseudomonas, Klebsiella, Proteus, Enterobacter, Providencia, Citrobacter	Urine, pus, sputum and blood	2015-16	NDM	-	93.94% and 80.31% isolates were sensitive to Polymyxin B and colistin	More than 77% isolates were resistant to piperacillin-tazobactam, amikacin, ciprofloxacin, Aztreonam, gentamicin	Manipal Teaching Hospital, Pokhara	14
<i>E. coli</i>	urine	2013	NDM-13	-	Colistin, fosfomycin	Ampicillin, Ampicillin-sulbactam, Aztreonam, Cefepime, imipenem, meropenem, Cefoselis, Cefotaxime, Cefoxitin, Cefpirome, Ceftazidime, Ceftriaxone, Cephadrine, Doripenem, ciprofloxacin, Gentamicin	TUTH*	15

Table 1: (Continued)

Isolate	specimen	Duration of study	NDM variant	Other resistance factors	Sensitive to	Resistant to	Study site	Ref
<i>K. pneumoniae</i>	-	2012	NDM-1	OXA-72 CTX-M-15, SHV-158, TEM-1, SHV-28, SHV-11, SHV-1, RmtC, RmtF, ArmA	-	Piperacillin, piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, aztreonam, amikacin, gentamicin	TUTH*	16
<i>K. Pneumoniae</i>	Blood	2012	NDM-1	-	-	Cefotaxime	Patan Hospital, Lalitpur	17
<i>Klebsiella</i> spp	Blood and urine		NDM-1	-	colistin	piperacillin-tazobactam, Ampicillin, Amikacin, Cefepime, Cefoxitin, Cefotaxim, Ceftriaxone, chloramphenicol, cefuroxime, ciprofloxacin, ertapenem, gentamicin, nalidixic acid, nitrofurantoin, ofloxacin, tobramycin	Patan Hospital, Lalitpur	18
<i>Acinetobacter baumannii</i>	-	2013-14	NDM-1	blaOXA-23, blaOXA-69, aacC1, aadA1, armA, blaOXA-32, blaOXA-420, blaPSE-1, aacA2, blaOXA-104, blaPER-7, blaOXA-94, aadB	colistin	Ceftazidime	TUTH*	19
<i>E. coli</i>	Sputum, urine and pus	2013-2014	NDM-1, NDM-3, NDM-4, NDM-5, NDM-7, NDM-12, NDM-13	blaCTX-M-15, blaOXA-181, blaTEM-166, rmtB, rmtC, aac(6)-Ib-cr, armA, aadA1, aadA2, aphA6, aadA5	colistin	Ceftazidime, Meropenem, Ciprofloxacin, Imipenem	TUTH*	20

*TUTH: Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal.

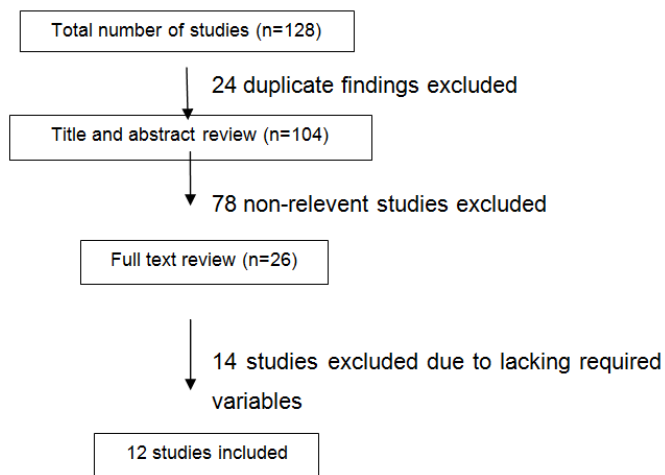


Figure 1: Flowchart for the selection process among identified studies.

All these facts conclude that NDM producing isolates of these two nations are comparable in many aspects.

DISCUSSION

Based on the review, NDM gene was reported in Nepal for the first time in 2012 among *E.coli*, *Providencia rettgeri*, *Pseudomonas* and *Klebsiella pneumoniae*. This gene has been detected in other various gram-negative isolates from the variety of clinical samples (Table 1).

There is a continuous increase in prevalence and spread of this gene in the world [6]. This increase in the occurrence of these isolates may be due to use of antibiotics recklessly, lack of proper training to laboratory staffs, inadequate administration of prophylactic sanitary procedures and absence of policies to contain hospital infections [30]. Many factors play role in its worldwide spread including its dissemination among various bacterial pathogens as well as in plasmids of the different type. However, other factors like epidemiological and environmental factors assisting its globalization and responsible genetic mechanism are not known [4]. The plasmid carrying NDM gene is auto-transmissible and versatile which may be the probable reason for its widespread dissemination among various microorganisms [31].

Many NDM producers were also positive for many other resistance genes including CTM-M, OXA, SHV, TEM, VIM, VEB, armA etc conferring resistance to the majority of members of different classes of antibiotics including penicillins, cepheims, monobactams, carbapenems, aminoglycosides, and quinolones. Co-existence of various other resistant determinants is common among these isolates including ESBL genes, carbapenemases etc [4, 32–35]. Co-production of such resistance gene is a matter of concern as it left the majority of available antibiotics ineffective. Isolates producing the variety of drug resistance genes in addition to NDM were

extremely drug-resistant as found in this study. Where the majority of the isolates were equipped with various carbapenemase genes causing carbapenem resistance, beta-lactamase genes causing almost all beta-lactams ineffective, 16S rRNA methylase and aminoglycoside acetyl/adenylyltransferase causing high resistance to aminoglycosides.

Very few treatment options were available for the isolates producing this gene in Nepal as most of them were sensitive only to colistin, fosfomycin, and tigecycline. However, there is a rise of resistance against colistin among these isolate from Nepal [11, 14] and other countries [36, 37] indicating the possibility of pan-drug resistance in these isolates. Similarly, the study of Li et al has reported tigecycline and colistin were the only treatment option for NDM positive *E. coli* and *K. pneumoniae* isolates [3]. Likewise, there are various reports of susceptibility of these isolates only to last line drugs [8, 35]. Hence, there is an urgent need to search for combination drugs that can treat such isolates effectively as new drug discovery takes a long time. There are number of studies reporting the effectiveness of combined therapy against such isolates: rifampin-meropenem-colistin combination was effective against VIM and NDM producing *K. pneumoniae* isolates [38], amikacin and colistin against NDM-5 and MCR-1 positive *E. coli* [39].

Screening of these isolates in communities and healthcare settings is very crucial for their treatment and proper control as there is a report of the hospital outbreak of NDM positive *K. pneumoniae* causing high mortality (75%) among septicemic children admitted at Patan Hospital, Lalitpur, Nepal in 2012 [17]. Early detection, proper training of the laboratory staffs and regular screening of hospital environment and equipments for such pathogens can prevent such high mortality in addition to prevention of their spread to various hospital wards. Various factors associated with these isolates which make them precarious are i) most plasmids bearing NDM are capable of rearrangement and are mobile posing possibility of transmission to the variety of bacterial pathogens, ii) lack of standard phenotypic methods for their regular detection, iii) probability of high prevalence among unknown symptomless carriers, iv) absence of an effective treatment option among available antibiotics [40].

Similarities between various characteristics of NDM producers between India and Nepal may be due to the similar type of health care practice, self medication, and reckless use of antibiotics. In addition to this, the source of these isolates may have same origin as there is huge flow of people between these two nations as medical tourists, workers, and pilgrims. Such visits may have contributed to unnoticed transmission of such pathogens between these two adjacent countries as there are evidences of transmission of NDM positive isolates as a result of medical tourism [41] and mass movement of pilgrims [42] and most reported cases are related to visit of South Asian countries.

Study of these isolates is focused primarily on Kathmandu valley which is not sufficient to know the status of these pathogens in this country. Hence, there is imminent need of surveillance study of these isolates throughout the country among clinical, asymptomatic carriers, and environmental samples as various studies have reported their detection from carriers [43, 44] and environmental isolates [31, 45]. As drug-resistant isolates in intestine and environment may act as a potential source of human infection, hence multisector studies and implementing suitable control measures are the only possible ways of their management. International collaboration is very crucial for the control of this global public health challenge posed by drug resistance as this is a great problem to overcome [2]. NDM producing gram-negative isolates are present among clinical isolates in Nepal. This study is significant as most of these isolates were highly drug resistant due to the co-production of various resistant determinants.

CONCLUSION

Regular screening, proper training to health practitioners, development of simple as well as effective phenotypic methods for their detection and prudent antibiotic use are crucial to contain their spread. Further study about these pathogens is necessary in the Indian subcontinent as it is considered a major reservoir area for these superbugs.

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Author Contributions

Surya Prasad Devkota – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Ashmita Paudel – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising

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Guarantor of Submission

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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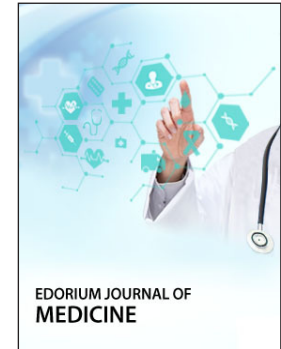
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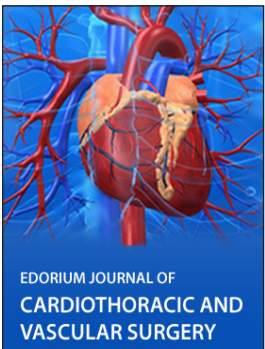
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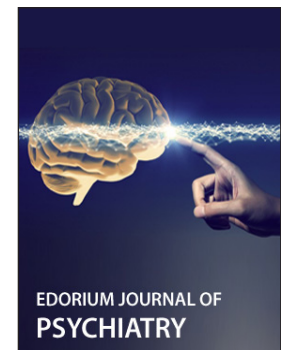
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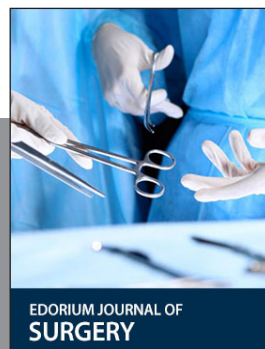
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