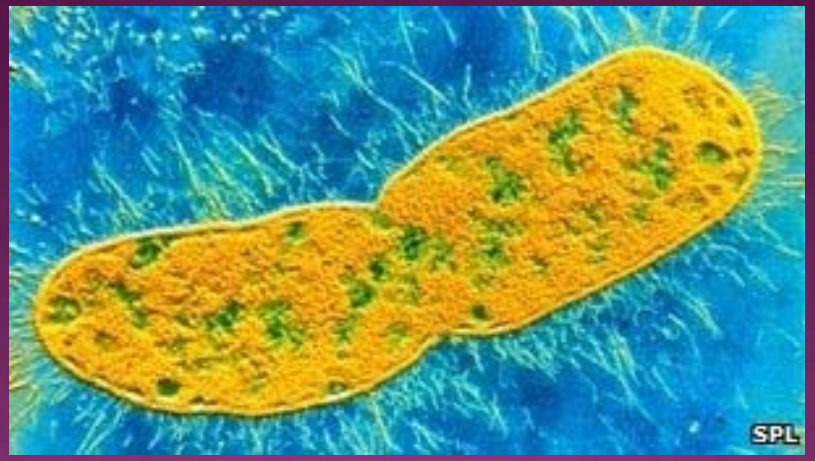


NDM-1 PRODUCING ENTEROBACTERIACEAE

Dr Vivien CHUANG
Associate Consultant
Infection Control Branch, Centre for Health Protection/
Infectious Disease Control and Training Center, Hospital Authority

WHAT IS NDM-1

NDM-1, which stands for

New Delhi Metallo-beta-lactamase-1

新德里金属酰胺酶

This is a **Carbapenemase** which neutralizes the activity of carbepenem antibiotics.

BACKGROUND

- Resistance to carbapenems is mediated by mechanisms:
  1. loss of outer membrane proteins, and
  2. production of carbapenemases that are capable of hydrolyzing the carbapenems.
- *Enterobacteriaceae Family:*

  Escherichieae (E.coli), Edwardsiella, Salmonella, Shigella, Citrobacter, Klebsiella, (K. pneumonia), Enterobacter, Morganella, Proteus, Serratia, Pantoea, Hafnia, Providencia, Yersinia

  - *Carbapenem resistant Enterobacteriaceae (CRE)*
  - *Carbapenemase producing Enterobacteriaceae*

CARBAPENEMASES & METALLO-β- LACTAMSE (MBL)

TABLE 4. Substrate and inhibition profiles of the carbapenemases

Molecular class	Functional group	Enzyme	Hydrolysis profile[a]					Inhibition profile[b]		Reference(s)
			Penicillins	Early cephalosporins	Extended-spectrum cephalosporins	Aztreonam	Carbapenems	EDTA	Clavulanic acid	
A	2f	NMC	+	+	+	+	+	−	+	124
		IMI	+	+	+	+	+	−	+	183
		SME	+	+	±	+	+	−	+	179
		KPC	+	+	+	+	+	−	+	4
		GES	+	+		−	±	−	+	174, 219
B1	3	IMP	+	+		−	+	+	−	224
		VIM	+			−	+	+	−	224
		GIM	+			−	+	+	−	224
		SPM	+			−	+	+	−	224
D	2d	OXA	+		±	−	±	−	±	225

[a] Symbols: +, strong hydrolysis (generally, k_{cat} of >2 s^{-1}); ±, weak hydrolysis (generally, k_{cat} of 0.5 to 2 s^{-1}); −, no measurable hydrolysis reported (generally, k_{cat} of <0.5 s^{-1}).

[b] Symbols: +, reported inhibition; ±, variable inhibition among β-lactamase family members; −, no inhibition reported.

Plasmid mediated

NDM-1

1ST CASE OF NDM-1 PRODUCING ENTEROBACTERIACEA

- A 59-year-old male, a **Swedish patient of Indian origin**
- Underlying diseases: Type 2 diabetes mellitus, multiple strokes
- Nov 07, he traveled to India
- 5 Dec 07, admitted to local hospital with a large gluteal abscess in Ludhiana, Punjab.
- He transferred to a hospital in New Dehli, he was operated on and where he developed a decubital ulcer
- Antibiotics given: Augumentin, metronidazole, amikacin, and gatifloxacin (all of them parenterally).

Antimicrobiol agent and Chemotherapy 2009; 53(12):5046-54

1ST CASE OF NDM-1 PRODUCING ENTEROBACTERIACEA

- 8 Jan 2008, he was referred to a hospital in Sweden
- 9 Jan 2008,

1. Urine sample: NDM-1 *K. penumoniae which is R to all β lactams, but S to Colistin*
2. *Deep wounds: E*SBL-positive *E. coli and carbapenem-susceptible Acinetobacter sp.*
3. External otitis fluid: *An* ESBL-positive *E. coli*

- 6 Mar 08, the patient was discharged to a nursing home.

Antimicrobiol agent and Chemotherapy 2009; 53(12):5046-54

1ST CASE OF NDM-1 PRODUCING ENTEROBACTERIACEA

- 1 Apr 08,

1. Urine sample: an ESBL-producing *K.pneumoniae*
2. *The* original carbapenem-resistant *K. pneumoniae isolate has never* been found in any other cultures of samples from the patient

- Fecal samples: *E. coli NDM-1*

NDM-1 K. penumoniae could not be recovered

Antimicrobiol agent and Chemotherapy 2009; 53(12):5046-54

WHY NDM-1 IMPORTANT

1. possible transfer of *blaNDM-1 in vivo either* from *K. pneumoniae to E. coli or vice versa, but more interestingly,* the plasmids carrying *blaNDM-1 in the two species are* of different sizes

2. This evidence would suggest that there is rearrangement in vivo which could result from either duplication and insertion, e.g. transposition or rolling circle replication from the smaller plasmid, or deletion from the larger plasmid

3. The plasmid carrying *blaNDM-1 also carries blaCMY-4 and the complex class 1 integron carrying several* antibiotic resistance-conferring gene

4. It has also shown itself to naturally have a broad host range.

IN VITRO EXPERIMENT DEMONSTRATION

- When the plasmid was transferred to *E. coli J53, the E. coli strain containing* pNDM-1 was resistant to all antibiotics except colistin and ciprofloxacin and was shown by blotting and PCR to carry *blaCMY-4, the ISCR region, and blaNDM-1*

CHARACTERISTICS OF NDM-1

- NDM-1 not only is a new subclass of the B1 group of MBLs but also possesses novel amino acids near the active site, suggesting that it has a novel structure
- NDM-1 possesses relatively high *Km and kcat values for both imipenem and meropenem (efficient hydrolysis profile)*

TABLE 2. Steady-state kinetic constants of NDM-1, IMP-1, and VIM-2

Compound	NDM-1			IMP-1[a]			VIM-2[b]		
	K_m (μM)	k_{cat} (s^{-1})	k_{cat}/K_m ($s^{-1}/\mu M$)	K_m (μM)	k_{cat} (s^{-1})	k_{cat}/K_m ($s^{-1}/\mu M$)	K_m (μM)	k_{cat} (s^{-1})	k_{cat}/K_m ($s^{-1}/\mu M$)
Penicillin G	16	11	0.68	520	320	0.62	49	56	1.14
Ampicillin	22	15	0.66	200	950	4.8	DNA		
Piperacillin	12	14	1.17	ND[c]	ND	ND	72	33	0.45
Cephalothin	10	4	0.40	21	48	2.4	44	57	1.28
Cefoxitin	49	1	0.02	8	16	2	24	3	0.12
Cefotaxime	10	6	0.58	4	1.3	0.35	32	28	0.86
Cefuroxime	8	5	0.61	37	8	0.22	22	12	0.55
Ceftazidime	181	5	0.03	44	8	0.18	98	89	0.90
Aztreonam	ND			>1,000	>0.01	<0.0001	ND	<0.5	ND
Cefepime	77	13	0.17	11	7	0.66	184	5	0.03
Imipenem	94	20	0.21	39	46	1.2	10	10	0.99
Meropenem	49	12	0.25	10	50	0.12	5	1	0.28
Clavulanic acid	ND			NR[d]			NR		

[a] From Spencer et al. (32).
[b] From Poirel et al. (23).
[c] ND, not detected.
[d] NR, not reported.

UPSURGE IN NDM-1 CASES IN INDIA, PAKISTAN, AND THE UK

www.thelancet.com/infection **Published online August 11, 2010 DOI:10.1016/S1473-3099(10)70143-2**

NDM-1 IN INDIA

Haryana

- 47 CRE (24%) of 198 Enterobacteriaceae were identified;
- OF 47 CRE, 26(55%) were NDM-1, and all were *K pneumoniae*

Chennai

- In 2009, 3521 (4%) Enterobacteriaceae were CRE
- Of these 141 CRE, 44 (31%) *were NDM-1*

19 *E coli,*
14 K pneumoniae,
7 Enterobacter cloacae,
2 Proteus spp,
1 Citrobacter freundii,
1 Klebsiella oxytoca)

Infection: community acquired UTI, pneumonia, and BSI
Age: mean 36 years (range was 4–66)

UK

- 2008: NDM-1isolate was first detected
- 2008–09: 37 NDM-1Enterobacteriaceae isolates. These were identified as

  K pneumoniae (21), E coli (7), Enterobacter spp (5), *Citrobacter freundii (2), Morganella morganii (1),* and *Providencia spp (1)*
- 2009: 32 (44%) of 73 carbapenemase-producing Enterobacteriaceae are NDM-1

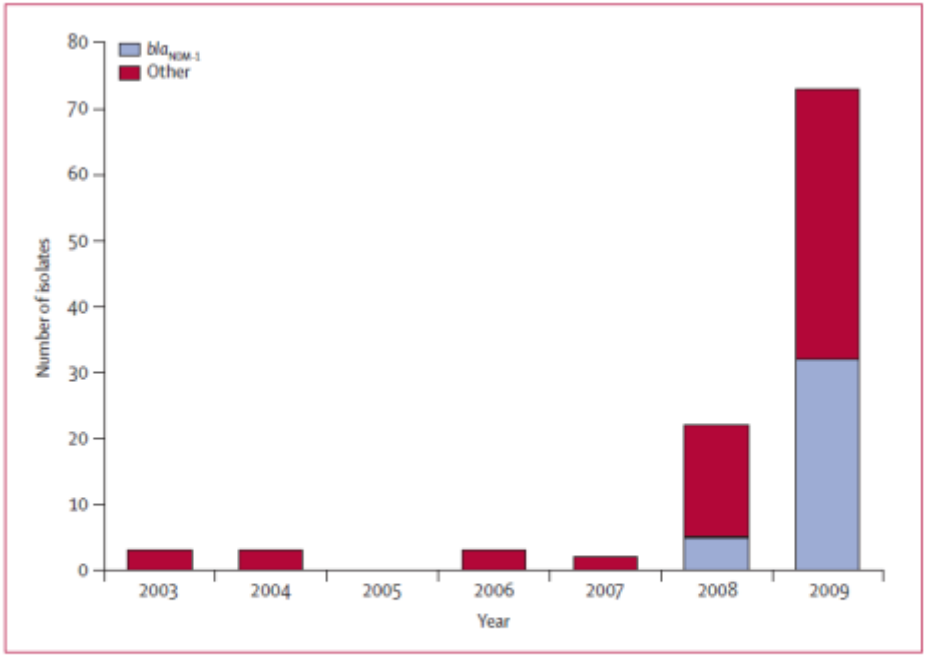


***Figure 1*: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency's national reference laboratory from 2003 to 2009**
The predominant gene is bla_{NDM-1}, which was first identified in 2008. The other group includes diverse producers of KPC, OXA-48, IMP, and VIM enzymes.

UK

- Body sites:

  urine (52%), blood (10%),burn or wound swab (13.8%), sputum (6.9%), central line tip (3%), throat swab (3%), or unknown specimens (10%)

- Mean age: 60 years (range 1–87)

- At least 17 (59%) patients had a history of travelling to India or Pakistan within 1 year, and 14 (48%) of them had been admitted to a hospital in these countries

	Chennai	Haryana	UK
Clonality	Non-clonal	Clonal (outbreak potential)	Non-clonal
Location of *bla*NDM-1 gene	Plasmid only	Plasmid only	Plasmid (chromosome, in situ movement of *bla*NDM-1 gene
	blaNDM-1 was carried on more than one plasmid		
Plasmid size	50 -350 kb	118 kb (54%) or 50 kb (36%).	80 - >500kb
plasmid movement between bacterial isolates	Evident by many plasmids of identical size in isolates collected from India and the UK		

	UK (n=37)		Chennai (n=44)		Haryana (n=26)	
	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*
Imipenem	32; 128	0%	64; 128	0%	32; 128	0%
Meropenem	32; 32	3%	32; >32	3%	>32; >32	3%
Piperacillin-tazobactam	>64; >64	0%	>64; >64	0%	>64; >64	0%
Cefotaxime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Ceftazidime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Cefpirome	>64; >64	0%	>64; >64	0%	>64; >64	0%
Aztreonam	>64; >64	11%	>64; >64	0%	>64; >64	8%
Ciprofloxacin	>8; >8	8%	>8; >8	8%	>8; >8	8%
Gentamicin	>32; >32	3%	>32; >32	3%	>32; >32	3%
Tobramycin	>32; >32	0%	>32; >32	0%	>32; >32	0%
Amikacin	>64; >64	0%	>64; >64	0%	>64; >64	0%
Minocycline	16; >32	0%	32; >32	0%	8; 16	0%
Tigecycline	1; 4	64%	4; 8	56%	1; 2	67%
Colistin	0·5; 8	89%†	1; 32	94%†	1; 2	100%†

MIC=minimum inhibitory concentration. *Susceptibility defined by British Society for Antimicrobial Chemotherapy and European Committee on Antimicrobial Susceptibility Testing breakpoints; doxycycline breakpoints were used for minocycline. †Colistin-resistant UK isolates were one isolate of *Morganella morganii* and one *Providencia* sp (both intrinsically-resistant species), also one *Klebsiella pneumoniae* and one *Enterobacter* sp.

Table: **Antibiotic susceptibilities for NDM-1-positive Enterobacteriaceae isolated in the UK and north (Chennai) and south India (Haryana)**

The NDM-1 superbug

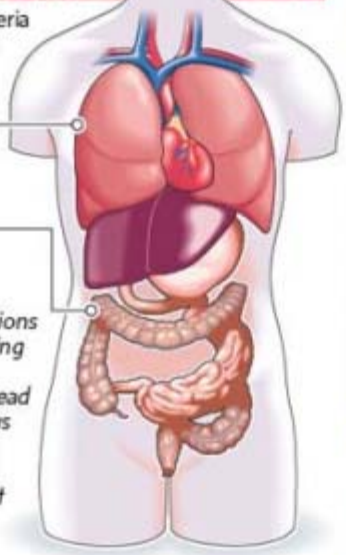
Experts are warning that a new type of drug-resistant superbug is emerging from India.
New Delhi metallo-ß-lactamase-1, or NDM-1, is an enzyme that can spread between different bacteria.

HOSTS

Two types of bacteria have been host to NDM-1:

Klebsiella pneumonia

E.coli



Both can lead to urinary tract infections and blood poisoning

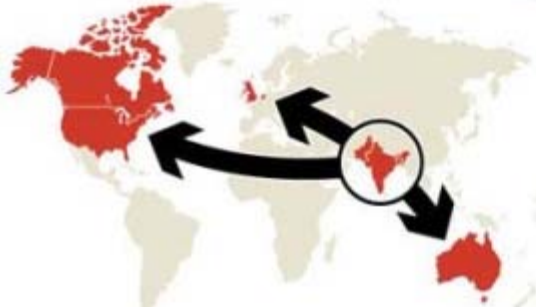
Enzyme could spread to more dangerous infections making them almost impossible to treat

INFECTION HOTSPOTS

Bacteria carrying NDM-1 can become resistant to ***carbapenem antibiotics*** *– a last line of defence against multi-resistant bacteria*

SPREAD

Widespread in India, Pakistan and Bangladesh. NDM-1 has now reached Britain, the United States, Canada, Australia and Netherlands



NINIAN CARTER/THE GLOBE AND MAIL/GRAPHIC NEWS ▮ SOURCES: THE LANCET; PA

DETECTION OF NDM-1 IN UNITED STATES, 2010

- Jan–Jun 10, 3 NDM-1 *Enterobacteriaceae* isolates *were identified from 3 U.S. states* at the CDC antimicrobial susceptibility laboratory

- These isolates, which include an *E. coli, K. pneumoniae, and E. cloacae, carry bla*NDM-*1,* which confers resistance to all beta-lactam agents, including aztreonam

- All three U.S. isolates were from patients who received recent medical care in India

MMWR / June 25, 2010 / Vol. 59 / No. 24

1ST CASE OF NDM-1 ISOLATE IN AUSTRALIA

- A man from Canberra, aged in his mid 50s, had elective plastic surgery in India in Sep 09. Complicated by a hypoxic brain injury, with ICU care for 4 weeks
- Transferred back to Canberra for ongoing hospital care.
- CSU on admission in Nov 09 : a heavy growth of multidrug-resistant *P. rettgeri* and *P. aeruginosa*.
- The *P. rettgeri* R to all b-lactam antibiotics, including meropenem, as well as to all aminoglycosides, ciprofloxacin, tigecycline and colistin. *The P. aeruginosa* was R to all antipseudomonal antibiotics except for colistin. P. rettgeri had 100% homology with blaNDM-1
- The patient was not given antibiotic therapy but the indwelling urinary catheter was changed and contact precautions were put in place.
- The patient cleared the organisms after 2 months, and since then has received ongoing inpatient care in the rehabilitation unit.

MJA 2010; 193 (1): 59

GLOBAL REPORTS OF NDM-1
AS OF 16 AUGUST 2010

Country	No of NDM-1 identified	Remark
India	70	1st reported case originated from India
Parkistan	73	
Bangladesh		
UK	37 (5 death)	More than 50% with travel history to India within 1 year and almost half of them being hospitalized in India
Germany		
Belgium	1	A Belgium citizen, of Pakistani origin, died in June.Leg wound after receiving wound care in Parkistan
France	1	Epi link to India
Netherland	1	Epi link to India
USA	3	All received medical care in India
Canada	2	Acciation with travel history to India
Australia	3	Received plastic surgery in India, travel to India
HK	1	A local resident of Indian ethnicity

SUMMARY

- Most *blaNDM-1 positive plasmids were* readily transferable and prone to rearrangement, losing or (more rarely) gaining DNA on transfer.
- This transmissibility and plasticity implies an alarming potential to spread and diversify among bacterial populations.
- Control Measures:

1. Vigilant lab surveillance for early detection
2. Contact precautions for identified case
3. HH
4. Rational use of antibiotics

END

THANK YOU