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BC Public Health Microbiology and Reference Laboratory PHSA Carbapenemase Producing Organisms: How BC Fairs Amidst Its Global Emergence.

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Objectives

- What are Carbapenemase Producing Organisms?
- Overview of global and national activities
- Update on BC activities
- Challenges and next steps









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What are Carbapenemase Producing Organisms (CPO)?

- Carbapenemases are a class of enzymes that inactivate carbapenem antibiotics by hydrolysing them.
- Carbapenem antibiotics, often referred to as "last resort antibiotics":
 - Imipenem
 - Meropenem
 - Ertapenem



 Carbapenemases most commonly in *E. coli* and *Klebsiella spp.*, (Enterobacterieaceae) but have also been found in other Gram-negative species.

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Terminology

- CRE: Carbapenem resistant Enterobacteriaceae (mechanism unknown)
- CPE: Carbapenemase producing Enterobacteriaceae (mechanism known)
- CPO: Carbapenemase producing organisms (Enterobacteriaceae plus other non-fermentors)
- Carbapenem: A broad-spectrum class of antibiotics
- Enterobacteriaceae: A family of Gram-Negative bacteria (e.g. *E. coli, Klebsiella pneumoniae*, etc)
- Non-fermentors: Pseudomonas sp, Acinetobacter sp, etc

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We are loosing are miracle drugs and research/industry are not rising up to the challenge











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ANTIBIOTIC APPROVALS: 1983-2011



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eta-lactamase Family

Molecular Class	Types
A	TEM, SHV, CTX-M KPC, GES, SMC, IMI, PER, NMC-A, SFO, SFC, BIC, IBC
В	NDM-1, IMP, VIM, GIM, SPM, SIM, DIM, AIM, KHM
С	CMY, ACT, FOX, MOX
D	OXA, PSE OXA-48



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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2009, p. 5046–5054 0066-4804/09/\$12.00 doi:10.1128/AAC.00774-09 Copyright © 2009, American Society for Microbiology. All Rights Reserved. Vol. 53, No. 12

Characterization of a New Metallo-β-Lactamase Gene, *bla*_{NDM-1}, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India[∇]

Dongeun Yong,^{1,2} Mark A. Toleman,² Christian G. Giske,³ Hyun S. Cho,⁴ Kristina Sundman,⁵ Kyungwon Lee,¹ and Timothy R. Walsh²*

Yonsei University College of Medicine, Research Institute of Antimicrobial Resistance, Seoul, Republic of Korea¹; Department of Medical Microbiology, Cardiff University, Cardiff, United Kingdom²; Clinical Microbiology, MTC—Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden³; Yonsei University College of Life Science and Biotechnology, Seoul, Republic of Korea⁴; and Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden⁵

- New metallo-² -lactamase (Ambler Class B), shares little with others in the same class
- NDM-1 found on plasmid therefore, transferable
- Other broad resistance genes carried on plasmid
- NDM resistant to all ² -lactams and many other antibiotics





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Transferable Carbapenemase genes (on plasmid)

 highly transmissible: Serious Infection Control implications



It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

 Can be shared between different species (Enterobacteriaceae, other gram-negative bacilli)





New Delhi Metallo-beta-lactamase (NDM-1)

- Reports in 2008 of Swedish and UK travelers to Indian subcontinent
- Since then, reports of high endemicity in Indian, Pakistan and Bangladesh hospitals
- NDM-1 genes in sewage and water reservoirs in some Indian cities
 - 51/171 (30%) waste water seepage
 - 2/50 (4%) communal drinking water samples

Walsh et al. The Lancet Infectious Diseases, 2011, 11: 355-62



CRE in UK 2003-2009



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Global Distribution NDM-1







First introductions of NDM-1 to Canada

- 76 yo female (*E. coli, K. pneumoniae* UTI) was hospitalized in India, direct transfer to a BC Hospital early 2010. First BC case. Mulvey et al. 2011. EID 17:103-6.
- 36 yo male hospitalized in India *E. coli* UTI, 2010. Successfully treated with fosfomycin/ert. Peirano et al. 2011. EID 17:242-4.
- 36 yo female Brampton, Ontario, *Kp* urine isolate, hospitalized in India. Tijet et al. 2011. EID 17:306-7.

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NDM in Canada: 2012-2013 Several reports on CRE outbreaks

- Borgia et al. Clinical Infectious Diseases
- 5 *K. pneumoniae* and *E.coli* all epi linked in a tertiary care community hospital in Brampton, Ont. No travel history.
- Chris Lowe et al., Infect Control Hosp Epidemiol.
- Transmission in a Toronto Hospital
- 2 index cases with NDM1 K. pneumoniae
- Transmission to 7 patients was identified
- Ahmed-Bentley et al., Antimicrob Agents Chemother.
- Outbreak in a Calgary Hospital
- Index case with hospitalization Hx in India
- Several MDR GNR organisms
- Transmission to 5 patients was identified; resulted in death of 1 patient from sepsis

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Notes from the Field

New Delhi Metallo-β-Lactamase–Producing *Escherichia coli* Associated with Endoscopic Retrograde Cholangiopancreatography — Illinois, 2013



Transmission via medical devices

- reviewed cleaning and disinfection process
- no lapse in protocol





NDM and KPC World-Wide



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Global Dissemination of KPC

- United States
 - KPC first reported in North Carolina in 2001-subsequent outbreaks and transmission of KPC-producing organisms reported in northeastern U.S
 - KPCs now in 42 states Dominant clone ST258 accounts for 70% of KPC isolates sent to CDC
 - KPC increased from 1.2% in 2001 to 4.2% in 2011
 - 2012, 4.6% of acute-care hospitals reported at least one CPE HAI
- Israel
 - Increased reports of KPC cases started in 2006
 - 8 hospitals and 5 long-term care centers with similar PFGE fingerprints
 - Genetic relation to U.S strains suggested strain exchange

MMWR Weekly 2013. 62(09);165-170. Gupta, N et al. 2011 CID.53:60-67. Provincial Health Services Authority PHSA Laboratories



KPC and NDM in the USA 3 NH ME WA V MT ND MN OR NY WI ≥MA ID SD MI WY RI PA IA NE OH NV IL. IN WV MD UT CO VA MO KY CA KS DC NC TN SC OK AZ AR NM GA AL MS LA TX AK FL PR KPC enzyme NDM enzyme

This map was last updated on December 31, 2013

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http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html





First introductions of KPC to Canada

- 1st report KPC in Ottawa (3 cases), 2008
 - 2 cases had travel history to USA
 - possible transmission

Goldfarb et al. (2009) JCM 47:1920-1922

• KPC strains and plasmids similar between NYC and Toronto Mataseje et al, (2011) JAC 66:1273–1277



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KPC Outbreaks in Canada

1 case from Toronto in 2008, no travel history Pillai et al, (2009) EID 15:827-828

Outbreak 1

- ICU 9 cases (3 pneumonia, 1 UTI, 1 SSI)
- E. coli (5), K. oxytoca (2), S. marcescens (2), and C. freundii (1)
- 4 deaths none attributed entirely to infection
 - 2012 Leung et al, Can J Infect Dis Med Micro

Outbreak 2

- 16 patients with KPC producing Enterobacter cloacae
- bla_{KPC} localized on multiple plasmids in a diverse non-clonal genetic background of *E. cloacae*
 - 2013 Haraoui, J Clin Micro

Now seeing outbreaks in Montreal

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Journal of Antimicrobial Chemotherapy

OXA-48-like carbapenemases: the phantom menace

Laurent Poirel*, Anaïs Potron and Patrice Nordmann

- First described in Turkey in 2004 Poirel et al. 2004. AAC. 48:15–22
- Focused around Mediterranean countries
- Outbreak of OXA-48 K. pneumoniae in France in 2010. 10 ICU patients in 2 months. 5 died. Cuzon et al. AAC 2011. 55(5):2420-2423.
- Found in 2/4 "puddles" sampled in Morocco Potron et al. 2011. AAC 2011. 55:5413-4.
- Most difficult to detect of the carbapenemases
 - Low MICs to carbapenem and cephalosporins
 - Under reporting?

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Letter

OXA-48-like carbapenemase-producing Enterobacteriaceae in Ottawa, Canada $\stackrel{
m imes}{}$

- 5 patients with healthcare outside of Canada
 - Syria, Egypt, St Lucia, Saudi Arabia, Australia and India
- No reports of outbreaks in Canada





CPE in Canada: CPHLN Data

KPC NDM OXA-48 SME Other



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CPE by Region in Canada: CPHLN Data







Treatment Options Enterobacteriaceae

- Carbapenems
 - e.g. Imipenem, Meropenem, etc
- ² -lactams (Ampicillin, Amoxicillin/Clavulanic, Cephalosporins)
- Fluoroquinolones
- Aminoglycosides
- Tetracyclines
- Nitrofurantoin

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- Colistin
- Chloramphenicol
- Tigecycline

Kus et al CMAJ 2010



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Treatment Options for CPE

- Carbapenems
 - e.g. Imipenem,
 Meropenem, etc
- ²-lactams (Ampicillin, Amoxicillin/Clavulanic, Cephalosporins)
- Fluoroquinolones
- Aminoglycosides
- Tetracyclines
- -- Nitrofurantoin



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- Colistin
- Chloramphenicol
- Tigecycline



Kus et al CMAJ 2010

BC's Response to this Emerging Pathogen

• Collaboration for Surveillance in BC since 2010

- BC Public Health Microbiology and Reference Laboratory (PHMRL)
- BC Association of Medical Microbiologists (BCAMM) and associated labs
- National Microbiology Laboratory (NML)
- PICNet

 Carbapenem-resistant Gram-negative Bacilli (CRGNB) ToolkitToolkit 2011 <u>http://www.picnet.ca/education-training/67/carbapenem-resistant-gram-negative-bacilli-(crgnb)-toolkit</u>







Frontline Laboratories

- Patient screening program as appropriate to the patient population and risk factors
 - Returning travelers from endemic regions
 - Patients with healthcare exposures in endemic regions
 - In-hospital contacts to known cases
- Specimen isolate screening methods
 - Follow up all carbapenem intermediate or resistant isolates with additional phenotypic tests (e.g. Etests, ROSCO disc tests, MAST disc tests, etc)
 - Send all potential CPO's to BCCDC lab



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Laboratory surveillance in BC (cont'd)

BC Public Health Lab

- Implemented molecular detection tools to confirm suspicious isolates
- Called positive results to submitting lab
 - travel history?
 - infection control interventions
- Repository for all identified isolates in BC
- Regular communications to update BC scenario via LabTrends <u>http://www.bccdc.ca/PHSALaboratories/PublicationsandReports/</u> <u>default.htm</u>







Laboratory surveillance in BC

- Isolates submitted to BC Public Health Lab since Oct 2010 (2008 by collection date)
 - Carbapenem intermediate and resistant isolates
- Multiplex PCR (NML and Hanson *et al*)
 - CPO
 - KPC, NDM, IMP, VIM, OXA-48, (SME)
 - ESBL
 - SHV, TEM, CTX-M, OXA-1, CMY-2
 - AmpC
 - CMY/MOX, CMY-2/LAT, DHA, ACC, MIR/ACT, FOX





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CPE PCR at BC Public Health Lab



>1000 isolates submitted to BCCDC from 2010 to December 2013 for testing.

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* Collection dates range from March, 2008-January 7, 2014.





Carbapenemase Producing Organisms by Species, 2008-Current*

NDM KPC VIM IMP OXA-48 SME





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CPE by Health Authority

■ NDM ■ KPC ■ VIM ■ OXA-48



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NDM+ Cases with Travel History

Cases with K. pneumoniae



Cases with Enterobacter

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Cases with E.coli, Citrobacter and Acinetobacter



• K. pneumoniae and Enterobacter

- Combination of nosocomial transmission and travel related
- E.coli, Citrobacter and Acinetobacter
 - Mostly travel related

From 2008-Sept 2013





1) NDM: antibiogram comparisons

 Can the comparison of isolate antibiograms be predictive of "clonality"



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2) NDM: genotype comparison

 Can the presence of other resistance genes detected by PCR predictive of "clonality"?

KPC	MQN	IMP	MIN	SHV	TEM	CTX-M	0XA-1	CMY-2	CMY-1	CMY-2/IAT	DHA	ACC	MIR/ACT	FOX	
Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	
Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	
Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	I
Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	F

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PFGE of Enterobacter cloacae



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Enterobacter cloacae genotype predicts clonality

KPC	MUN	IMP	MIN	SHV	TEM	CTX-M	0XA-1	CMY-2	CMY-1	CMY-2/LAT	DHA	ACC	MIR/ACT	FOX	
Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	
Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	
Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	I
Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Pos	Neg	Neg	Neg	ł



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PFGE-Xbal

PFGE of K. pneumoniae

<u></u> Pt / Year	GN ⁻ GNTP ID AbG ID Trav Hx
Pt 8 2011	KPC N Y US multip adm
Pt 8 2011	КРС
Pt 9 2012	NDN Y
Pt 38 2013	NDN N
Pt 9 2011	NDN Y Y
Pt 38 2013	NDN
Pt 9 2011	
Pt 6 2011	NDN Y N Y India, multip adm
Pt 6 2011	NDM
Pt 32 2012	KPC
Pt 35 2012	NDM
Pt 23 2012	NDN
Pt 20 2012	NDM N N
Pt 18 2012	NDM
Pt 3 2010	NDM
Pt 22 2012	NDN
Pt 29 2012	NDNI N
Pt 39 2013	NDM
Pt 2 2009	NDM Y Y India
Pt 2 2008	NDN
Pt 33 2012	NDM
Pt 37 2013	NDM
Pi 28 2012	NDM
Pt 5 2010	KPC, VI
Pt 5 2010	KPC, VIIvi
Pt 30 2012	NDM
Pt 7 2011	NDM



Plasmid-mediated transmission

Pt/ Year	Species	KPC	MDN	IMP	MIN	SHV	TEM	CTX-M	OXA-1	CMY-2	CMY-1	CMY-2/LAT	DHA	ACC	MIR/ACT	FOX
Pt 16, 2011	E. coli	Neg	Pos	Neg	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Pos	Neg	Neg	Neg	Neg
Pt 16, 2011	E. cloacae	Neg	Pos	Neg	Neg	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Pt 22, 2012	E. coli	Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Pt 22, 2012	E. cloacae	Neg	Pos	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Pt 22, 2012	K. pneumoniae	Neg	Pos	Neg	Neg	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg





BCCDC Public Health Microbiology & Reference Laboratory



Home » News » British Columbia



B.C. steps up battle with 'nightmare bacteria' cluster

WENDY STUECK

VANCOUVER — The Globe and Mail Published Thursday, Jan. 23 2014, 9:00 AM EST Last updated Friday, Jan. 24 2014, 9:31 PM EST



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How are these organisms transmitted?

- 1. Patient-to-patient
- 2. Shared Health Care equipment
- 3. Environmental Contact (environmental reservoirs)
- 4. Health care workers (Primarily hands)





How to prevent spread

MAJOR ARTICLE

Containment of a Country-wide Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* in Israeli Hospitals via a Nationally Implemented Intervention

Mitchell J. Schwaber,¹ Boaz Lev,² Avi Israeli,² Ester Solter,¹ Gill Smollan,¹ Bina Rubinovitch,¹ Itamar Shalit,¹ Yehuda Carmeli,¹ and the Israel Carbapenem-Resistant Enterobacteriaceae Working Group^a

¹National Center for Infection Control, Israel Ministry of Health, Tel Aviv, and ²Israel Ministry of Health, Jerusalem, Israel

Screening, Testing and Surveillance for Antibiotic-Resistant Organisms (AROs)

In All Health Care Settings



Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE)

2012 CRE Toolkit



Management of Carbapenem Resistant Gram-Negative Bacilli (CRGNB)

Provincial Infectious Diseases Advisory Committee (PIDAC)

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Risk factors for Colonization and Infection with CPE

Risk factors for acquisition of CPE

- prolonged hospitalization
- Poor functional status
- ICU stay
- invasive devices
- Immunosuppresion
- multiple antibiotic agents

Risk factors for infection once colonized with CPE

- Previous invasive procedure
- Diabetes mellitus
- Solid organ tumor
- Tracheostomy
- Urinary catheter
- Prior exposure to antipseudomonal penicillin

If colonized with CPE, 9-47% of patients may develop infection





CPE Measures Implemented at Affected Units

- Screening/Active surveillance
 - On admission to Unit
 - Weekly point prevalence
 - All contacts of suspect or confirmed cases, at 0, 7 and 21 days
- Precautions
 - Private room and staff cohorting and dedicated equipment
- Cohorting of patients and staff
 - "CPE" nursing assignments & dedicated ward
 - Hand hygiene & PPE (goal: 100%)
 - Weekly audits
- Antimicrobial stewardship

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CPE Measures Implemented at Affected Units (2)

- Avoid discarding any bodily fluids in sinks
- Cleaning
 - Enhanced cleaning including daily 2nd clean of high touch surfaces in affected rooms/units
 - Use hydrogen peroxide
 - Terminal clean on discharge of colonized patients:
 - Discard all supplies, terminal clean, audit of clean
- Daily CHG baths for all colonized patients.







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NDM-positive Isolates from Location X in FHA facility 2013







Enterobacteriaceae with NDM in 2013 (Total=52)



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Infection Control Processes "in the works"

- Region-wide screening for all admitted patients
 - Question: "Have you been hospitalized or had renal dialysis outside of Canada anytime in the previous 6 months?"
 - If yes: patient will have rectal screen for CPE
- Flagging of contacts who leave hospital before 21 days of CRE screening for screening on readmission







FHA CPE Activity

 No new cases since mid-January



 Increase specimen volume for the lab



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Next Steps and Challenges

- Better and faster testing
 - Develop Real-time PCR method for screening specimens directly
- Maintain aggressive infection control state & CPE alerts between facilities
- Continued Provincial level surveillance with infection control data
 - Collaboration with PICNet
- Further explore genomic characteristics of BC strains and transmission behaviour
 - Whole Genome Sequencing





Summary

- CPE are an emerging pathogen with global spread, now in Canada
- CPE can spread within institutions
- The most vulnerable patients are the most at risk to become colonized and infected
- Treatment of infections is complex
- Control of spread requires full compliance with precautions and antibiotic stewardship







Summary- BC specific

- CPE present in BC. Most commonly NDM and OXA-48
 - Most are identified in hospital setting
- CPE initially introduced to BC facilities from returning travelers to endemi2012: Evidence of nosocomial transmission in BC. Mostly due to NDM+ *K. pneumoniae* and *Enterobacter cloacae*
- Characterization of BC strains suggests clonal nature of *Enterobacter cloacae* spread, but also plasmid-mediated for *K. pneumoniae.*
- Use of "genotypic" patterns predictive of clonality for *Enterobacter* cloacae, but not for *K. pneumoniae*
- Clusters of CPE cases in facilities responding to enhanced screening and infection control interventions







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Dr. Inna Sekirov

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Thank you!







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Age Distribution for CPE





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Identified Organisms Harbouring NDM-1

- E. coli (ST131), K. pneumoniae, K. oxytoca, C. freundii, E. cloacae, E. aerogenes, M. morganii, Proteus spp., Providencia spp., and Salmonella Seftenberg
- Achromobacter spp
- Aeromonas caviae
- Acinetobacter baumannii
- Kingella denitrificans
- Pseudomonas aeruginosa, P. putida, P. pseudoalcaligenes, P. oryzihabitans
- Stenotrophomonas maltophilia
- Sutonella indologenes
- Vibrio cholerae
- Shigella boydii

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