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NEW PARADIGM AHEAD
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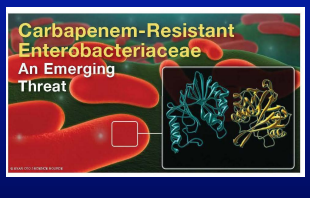
Making Sense of Alphabet Soup: Antimicrobial Resistance in Gram-Negative Bacilli



Andrew E. Simor, MD, FRCPC, FACP
Sunnybrook Health Sciences Centre
and the University of Toronto

www.webbertraining.com June 20, 2017

Disclosures

I have received grants, and served as a consultant on Advisory Boards for:

- Merck Canada Inc.

I will not be discussing ESBLs or fluoroquinolone resistance in GNBs

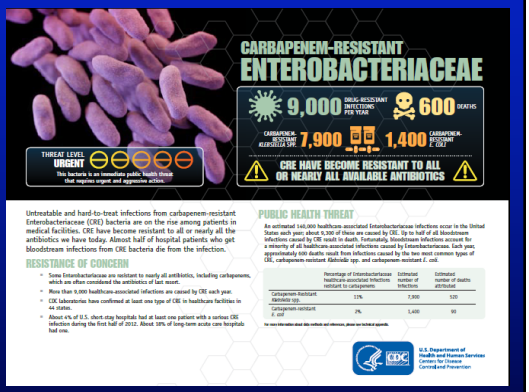
Objectives

- to understand the mechanisms of carbapenem resistance in GNBs
- to appreciate the epidemiology, risks, and clinical significance of carbapenem resistance
- to consider evidence-based infection prevention and control strategies to limit the emergence and spread of carbapenem-resistant GNBs

Why Do We Care (about GNB resistance)?

- GNBs are major causes of infection, especially nosocomial or healthcare-associated
- GNB infections are associated with significant morbidity and mortality
- increasing incidence of multidrug-resistant GNB; treatment options are often limited

Antibiotic Resistance Threats



CDC, 2013

NDM-1

Antimicrobial	Antimicrobial Susceptibilities MIC_{90}(mg/L)	% Susceptible
Imipenem	128	0
Meropenem	32	3
Pip/Tazo	>64	0
Cefotaxime	>256	0
Ceftazidime	>256	0
Ciprofloxacin	>8	8
Tobramycin	>32	0
Amikacin	>64	0
Tigecycline	4	67
Colistin	8	100

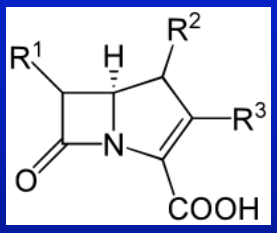
Kumarasamy, Lancet Infect Dis 2010

Carbapenems
"The Big Gun"

- ertapenem
- imipenem
- meropenem
- doripenem

Carbapenems

- Active against most:
  - Streptococci
  - Enterococci
  - MSSA
  - Enterobacteriaceae
  - GNB afermenters (eg. *Pseudomonas*)
  - Anaerobes
- Ertapenem is ***not*** active against *Pseudomonas*



Carbapenems
Common Indications

Syndrome	Pathogen
• sepsis NYD	• polymicrobial (GNB + anaerobes)
• HAP, VAP	• ESBLs
• intra-abd sepsis	• *P. aeruginosa*
	• *Acinetobacter* spp.

Carbapenem Resistance in GNB

- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.
- *Enterobacteriaceae*

Carbapenem Resistance in *Pseudomonas* and Acinetobacter

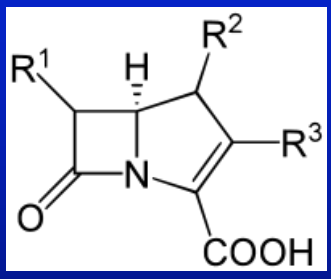
- In the US, 15-22% of *P. aeruginosa* and 21-48% of *Acinetobacter* spp. are carbapenem-resistant
- In Canada, 10-24% of *P. aeruginosa* and <10% of *Acinetobacter* are carbapenem-resistant

Davies, J Antimicrob Chemother 2011; McCracken, Diagn Microbiol Infect Dis 2011; Mataseje, J Antimicrob Chemother 2012; Zilberberg, J Hosp Med 2016

Mechanisms of Carbapenem Resistance

- changes in OMPs (permeability barrier: porin loss + ESBL/AmpC ß-lactamase); especially in *Pseudomonas*, or if isolate is R only to ertapenem and not to other carbapenems
- carbapenemases

Carbapenemases



Enzymes that hydrolyze carbapenem antibiotics (and typically also most other β-lactams and β-lactamase inhibitors); may be chromosomally encoded or more commonly plasmid-mediated

Carbapenemases ("alphabet soup")

Class A (serine)
- SME (*Serratia*)
- IMI (*Enterobacter*)
- GES (*Pseudomonas*)
- KPC (*Klebsiella*)

Class B (MBL)
- VIM (*Pseudomonas*)
- IMP, SPM, GIM, SIM
- NDM

Class D carbapenemase
- OXA (*Acinetobacter*)
- OXA-48 (*Enterobacteriaceae*)

CPE in Europe, 2014

Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study

Hajo Grundmann*, Corinna Glasner*, Barbara Albiger, David M Aanensen, Chris T Tomlinson, Arjana Tambić Andrasević, Rafael Cantón, Yehuda Carmeli, Alexander W Friedrich, Christian G Giske, Youri Glupczynski, Marek Gniadkowski, David M Livermore, Patrice Nordmann, Laurent Poirel, Gian M Rossolini, Harald Seifert, Alkiviadis Vatopoulos, Timothy Walsh, Neil Woodford, Dominique L Monnet, and the European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) Working Group†

Summary

Background Gaps in the diagnostic capacity and heterogeneity of national surveillance and reporting standards in Europe make it difficult to contain carbapenemase-producing Enterobacteriaceae. We report the development of a consistent sampling framework and the results of the first structured survey on the occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in European hospitals.

Methods National expert laboratories recruited hospitals with diagnostic capacities, who collected the first ten carbapenem non-susceptible clinical isolates of *K pneumoniae* or *E coli* and ten susceptible same-species comparator isolates and pertinent patient and hospital information. Isolates and data were relayed back to national expert laboratories, which made laboratory-substantiated information available for central analysis.

Findings Between Nov 1, 2013, and April 30, 2014, 455 sentinel hospitals in 36 countries submitted 2703 clinical isolates (2301[85%] *K pneumoniae* and 402 (15%) *E coli*). 850 (37%) of 2301 *K pneumoniae* samples and 77 (19%) of 402 *E coli* samples were carbapenemase (KPC, NDM, OXA-48-like, or VIM) producers. The ratio of *K pneumoniae* to *E coli* was 11:1. 1·3 patients per 10000 hospital admissions had positive clinical specimens. Prevalence differed greatly, with the highest rates in Mediterranean and Balkan countries. Carbapenemase-producing *K pneumoniae* isolates showed high resistance to last-line antibiotics.

Interpretation This initiative shows an encouraging commitment by all participants, and suggests that challenges in the establishment of a continent-wide enhanced sentinel surveillance for carbapenemase-producing Enterobacteriaceae can be overcome. Strengthening infection control efforts in hospitals is crucial for controlling spread through local and national health care networks.

- 455 hospitals in 36 countries
- 402 E. coli: 19% CPE
- 2,301 *K. pneumoniae*: 3.7% CPE
- mainly KPC, NDM, OXA-48, VIM

Grundmann, Lancet Infect Dis 2017

CPEs in Canada

JOURNAL OF CLINICAL MICROBIOLOGY, June 2009, p. 1920–1922 Vol. 47, No. 6
0095-1137/09/$08.00+0 doi:10.1128/JCM.00008-09
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Detection of Plasmid-Mediated KPC-Producing *Klebsiella pneumoniae* in Ottawa, Canada: Evidence of Intrahospital Transmission[▽]

David Goldfarb,[1,3] Sarah-Beth Harvey,[2] Kelsi Jessamine,[2] Peter Jessamine,[1,2,3] Baldwin Toye,[1,2,3] and Marc Desjardins[1,2,3,*]

Division of Microbiology, Department of Pathology and Laboratory Medicine, the Ottawa Hospital,[1] the Ottawa Hospital Research Institute,[2] and the University of Ottawa,[3] Ottawa, Ontario, Canada

Received 16 January 2009/Returned for modification 18 March 2009/Accepted 28 March 2009

Klebsiella pneumoniae **isolates from three patients admitted to the Ottawa Hospital, a 1,040-bed teaching hospital, were found to contain the plasmid-borne *K. pneumoniae* carbapenemase (KPC)-producing *bla* gene (*bla*$_{KPC}$). There was evidence of person-to-person transmission for two patients. Screening of 186 clinical isolates revealed no additional *bla*$_{KPC}$-containing isolates.**

CMAJ RESEARCH

CASE REPORT

New Delhi metallo-β-lactamase-1: local acquisition in Ontario, Canada, and challenges in detection

Julianne V. Kus PhD, Manal Tadros MBBS PhD, Andrew Simor MD, Donald E. Low MD, Allison J. McGeer MSc MD, Barbara M. Willey ART, Cindy Larocque MLT, Karen Pike MLT, Iris-Ann Edwards MLT, Helen Dedier MLT, Roberto Melano PhD, David A. Boyd MSc, Michael R. Mulvey PhD, Lisa Louie ART, Christopher Okeahialam MSc CIC, Mark Bayley MD, Cynthia Whitehead MSc(H) MD, Denyse Richardson MEd MD, Lesley Carr MD, Fatema Jinnah MBBS MSc, Susan M. Poutanen MD MPH

See related commentary by Walsh on page 1240 and at www.cmaj.ca/lookup/doi/10.1503/cmaj.111100.

ABSTRACT

New Delhi metallo-β-lactamase-1 (NDM-1) is a recently identified metallo-β-lactamase that confers resistance to carbapenems and all other β-lactam antibiotics, with the exception of aztreonam. NDM-1 is also associated with resistance to many other classes of antibiotics. The enzyme was first identified in organisms isolated from a patient in Sweden who had previously received medical treatment in India, but it is now recognized as endemic throughout India and Pakistan and has spread worldwide. The gene encoding NDM-1 has been found predominantly in *Escherichia coli* and *Klebsiella pneumoniae*. We describe the isolation NDM-1–producing organisms from two patients in Toronto, Ontario. To the best of our knowledge, this is the first report of an organism producing NDM-1 that was locally acquired in Canada. We also discuss the evidence that NDM-1 can affect bacterial species other than *E. coli* and *K. pneumoniae*, the limited options for treatment and the difficulty laboratories face in detecting organisms that produce NDM-1.

Competing interests: Allison McGeer is a member of the board for Bayer and Pfizer and has received grants and speaker fees from same. No competing interests were declared by the other authors.

This article has been peer reviewed.

Correspondence to: Dr. Susan M. Poutanen, spoutanen@mtsinai.on.ca

CMAJ 2011. DOI:10.1503/cmaj.110477

ORIGINAL ARTICLE

First Canadian outbreak of Enterobacteriaceae-expressing *Klebsiella pneumoniae* carbapenemase type 3

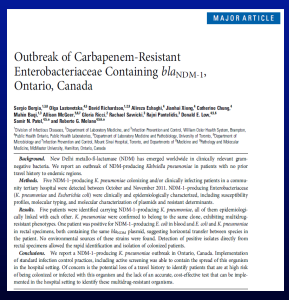
Victor Leung MD[1], Vivian G Loo MD MSc[2], Charles Frenette MD[3], Marc-Christian Domingo MD[3], Anne-Marie Bourgault MD[3], Michael R Mulvey PhD[4], Hugh G Rotstein MD[3]

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY JANUARY 2012, VOL. 33, NO. 1

ORIGINAL ARTICLE

Nosocomial Transmission of New Delhi Metallo-β-Lactamase-1-Producing *Klebsiella pneumoniae* in Toronto, Canada

Christopher F. Lowe, MD,[1] Julianne V. Kus, PhD,[2] Natasha Sak, BASc,[2] Sandra Callery, MHSc,[2] Lisa Louie, ART,[2] Mohammed A. Khan, PhD,[2] Mary Vearncombe, MD,[3] Andrew E. Simor, MD[3,4]



MAJOR ARTICLE

Outbreak of Carbapenem-Resistant Enterobacteriaceae Containing *bla*$_{NDM-1}$, Ontario, Canada

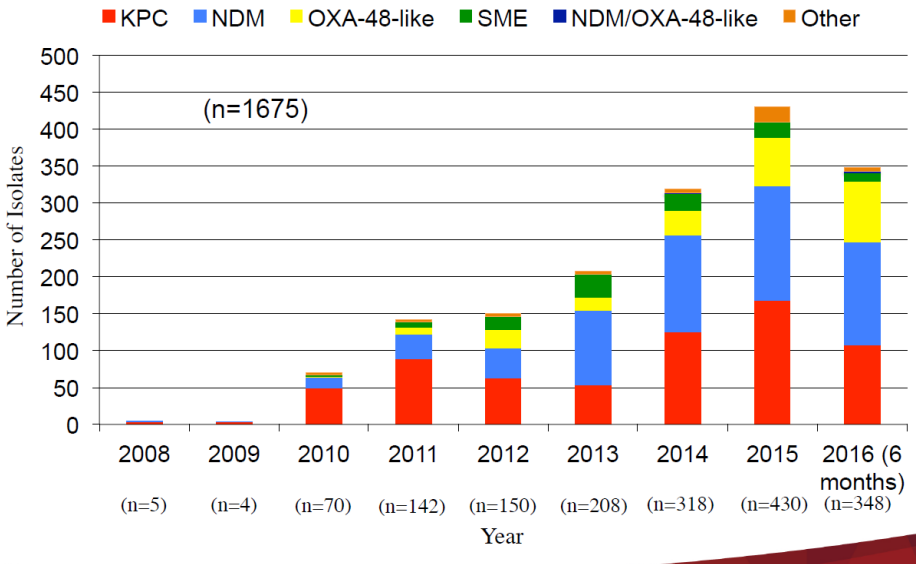
Teleclass broadcast sponsored by Sealed Air Diversey Care (www.sealedair.com)
A Webber Training Teleclass
www.webbertraining.com

CPE Surveillance in Canada
CNISP 2010-2014

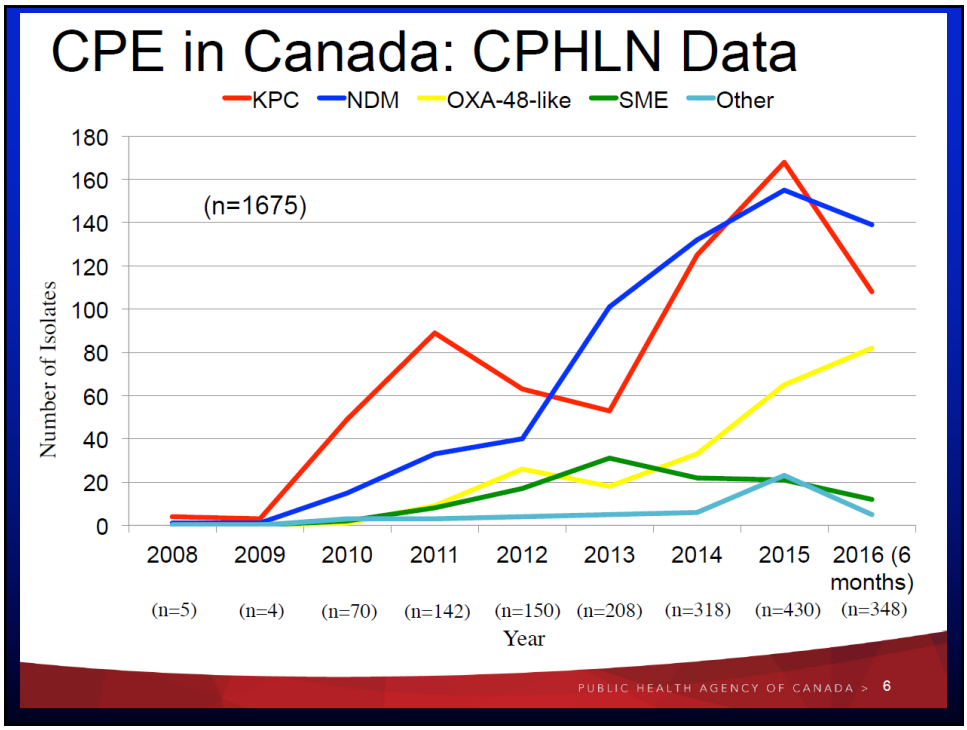
- **Overall incidence:**
  - **0.07 per 1,000 admissions**
  - **0.09 per 10,000 patient-days**
  - **(about 1/100th of MRSA rates)**
  - **< 1% of *E. coli* or *Klebsiella***

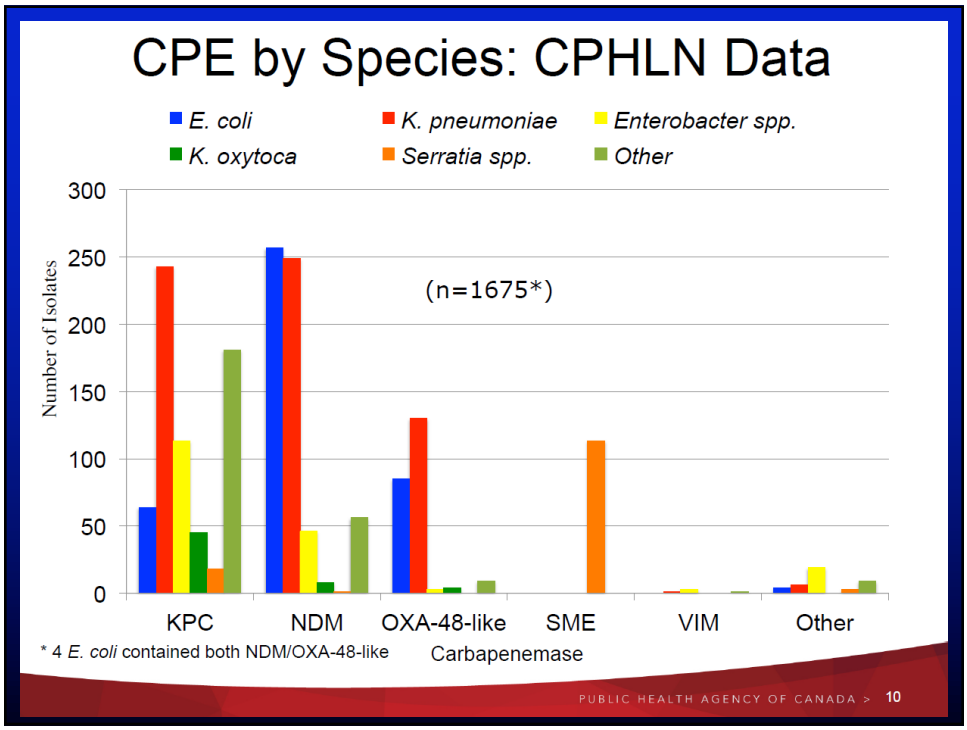
Mataseje, Antimicrob Agents Chemother 2017

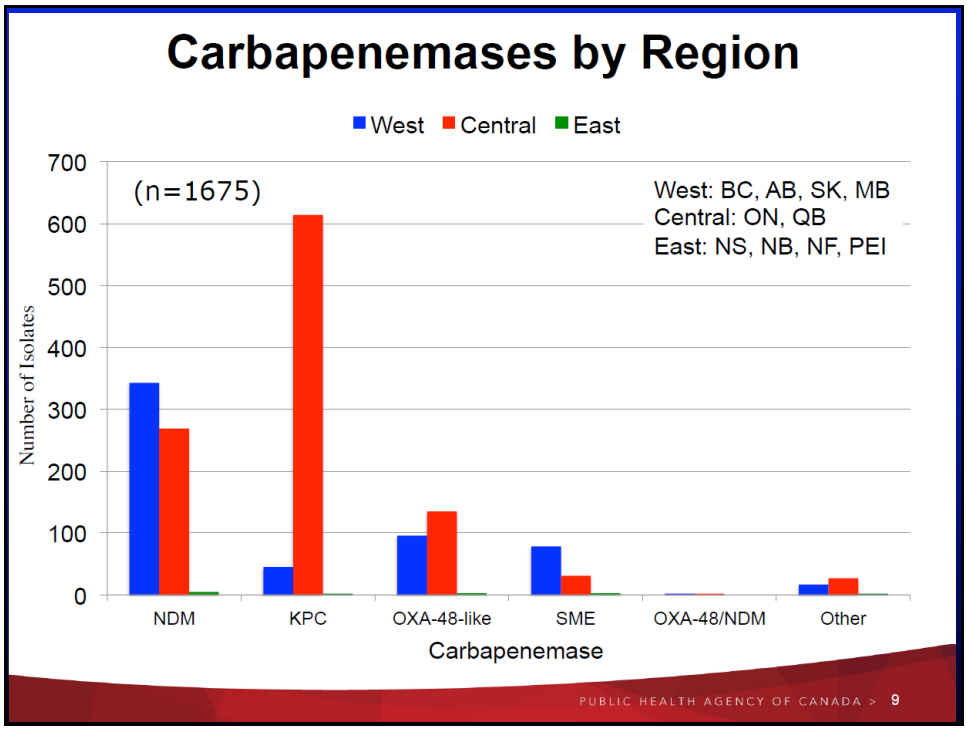
CPE in Canada: CPHLN Data



PUBLIC HEALTH AGENCY OF CANADA > 5

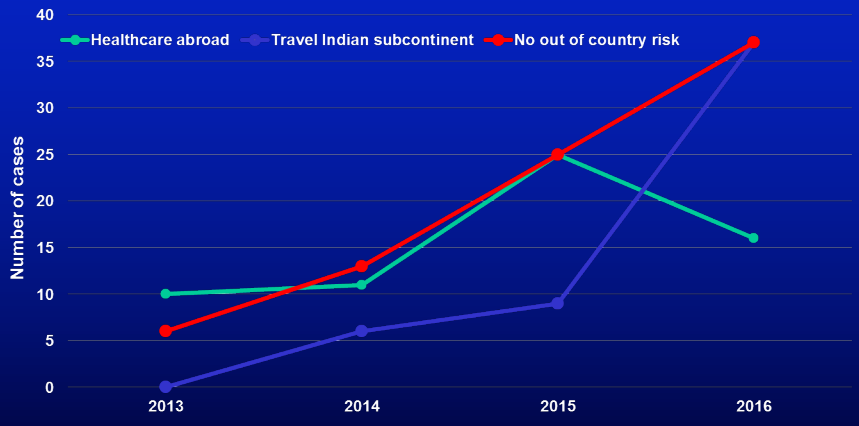

CPE in Canada: CPHLN Data
KPC
NDM
OXA-48-like
SME
Other
(n=1675)
Number of Isolates
180
160
140
120
100
80
60
40
20
0
2008
2009
2010
2011
2012
2013
2014
2015
2016 (6 months)
(n=5)
(n=4)
(n=70)
(n=142)
(n=150)
(n=208)
(n=318)
(n=430)
(n=348)
Year
PUBLIC HEALTH AGENCY OF CANADA > 6


CPE by Species: CPHLN Data
E. coli
K. pneumoniae
Enterobacter spp.
K. oxytoca
Serratia spp.
Other
(n=1675*)
Number of Isolates
300
250
200
150
100
50
0
KPC
NDM
OXA-48-like
SME
VIM
Other
* 4 E. coli contained both NDM/OXA-48-like
Carbapenemase
PUBLIC HEALTH AGENCY OF CANADA > 10


Carbapenemases by Region
West
Central
East
(n=1675)
West: BC, AB, SK, MB
Central: ON, QB
East: NS, NB, NF, PEI
Number of Isolates
700
600
500
400
300
200
100
0
NDM
KPC
OXA-48-like
SME
OXA-48/NDM
Other
Carbapenemase
PUBLIC HEALTH AGENCY OF CANADA > 9


Travel Related
Antibiotic Resistance
including Medical Tourism
medical
Tourism

CPE in Toronto/Peel, colonized/infected patients



TIBDN, 2017 (A. McGeer)

CPE Risk Factors

- Similar as for other AROs:
  - recent hospitalization
  - ICU admission
  - invasive medical devices
  - antibiotic exposure
  - chronic wounds

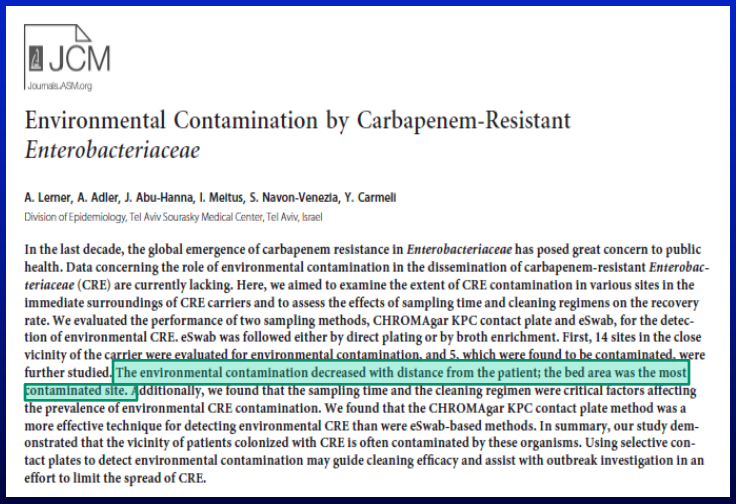
Savard, Infect Control Hosp Epidemiol 2013

CPE Fecal Carriage

- mean duration of CPE fecal carriage post-hospital discharge: 387 days; 39% still carrying CPE at 1-year post-discharge
- risks associated with prolonged carriage:
  - repeat hospitalization
  - CPE in clinical culture
    (not just screening cultures)

Zimmerman, Am J Infect Control 2013

Environmental contamination of the hospital environment is common



JCM
Journals.ASM.org

Environmental Contamination by Carbapenem-Resistant *Enterobacteriaceae*

A. Lerner, A. Adler, J. Abu-Hanna, I. Meitus, S. Navon-Venezia, Y. Carmeli
Division of Epidemiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

In the last decade, the global emergence of carbapenem resistance in *Enterobacteriaceae* has posed great concern to public health. Data concerning the role of environmental contamination in the dissemination of carbapenem-resistant *Enterobacteriaceae* (CRE) are currently lacking. Here, we aimed to examine the extent of CRE contamination in various sites in the immediate surroundings of CRE carriers and to assess the effects of sampling time and cleaning regimens on the recovery rate. We evaluated the performance of two sampling methods, CHROMAgar KPC contact plate and eSwab, for the detection of environmental CRE. eSwab was followed either by direct plating or by broth enrichment. First, 14 sites in the close vicinity of the carrier were evaluated for environmental contamination, and 5, which were found to be contaminated, were further studied. The environmental contamination decreased with distance from the patient; the bed area was the most contaminated site. Additionally, we found that the sampling time and the cleaning regimen were critical factors affecting the prevalence of environmental CRE contamination. We found that the CHROMAgar KPC contact plate method was a more effective technique for detecting environmental CRE than were eSwab-based methods. In summary, our study demonstrated that the vicinity of patients colonized with CRE is often contaminated by these organisms. Using selective contact plates to detect environmental contamination may guide cleaning efficacy and assist with outbreak investigation in an effort to limit the spread of CRE.

Lerner, J Clin Microbiol 2013

Contaminated Hospital Sinks

- contaminated handwashing sinks identified as a source/reservoir for ongoing transmission of CPEs

Lowe, Infect Control Hosp Epidemiol 2013
Vergara-Lopez, Clin Microbiol Infect 2013;
Leitner, Antimicrob Agents Chemother 2015

CRE Transmission via Duodenescopes

Research

Original Investigation

New Delhi Metallo-β-Lactamase–Producing Carbapenem-Resistant *Escherichia coli* Associated With Exposure to Duodenoscopes

Lauren Epstein, MD, MSc; Jennifer C. Hunter, DrPH; M. Allison Arwady, MD; Victoria Tsai, MPH; Linda Stein, MPH; Marguerite Grboyianis, MPA; Mabel Frias, MPH; Alice Y. Guh, MD; Alison S. Laufer, PhD; Stephanie Black, MD; Massimo Pacilli, MS; Heather Moulton-Meissner, PhD; J. Kamile Rasheed, PhD; Johnnetta J. Awilan, BS; Brandon Kitchel, MS; Brandi M. Limbago, PhD; Duncan MacCannell, PhD; David Lonsway, PhD; Judith Noble-Wang, PhD; Judith Conway, RN; Craig Conover, MD; Michael Vernon, DrPH; Alexander J. Kallen, MD

Editorial page 1605

IMPORTANCE Carbapenem-resistant Enterobacteriaceae (CRE) producing the New Delhi metallo-β-lactamase (NDM) are rare in the United States, but have the potential to add to the increasing CRE burden. Previous NDM-producing CRE clusters have been attributed to person-to-person transmission in health care facilities.

OBJECTIVE To identify a source for, and interrupt transmission of, NDM-producing CRE in a northeastern Illinois hospital.

DESIGN, SETTING, AND PARTICIPANTS Outbreak investigation among 39 case patients at a tertiary care hospital in northeastern Illinois, including a case-control study, infection control assessment, and collection of environmental and device cultures; patient and environmental isolate relatedness was evaluated with pulsed-field gel electrophoresis (PFGE). Following identification of a likely source, targeted patient notification and CRE screening cultures were performed.

MAIN OUTCOMES AND MEASURES Association between exposure and acquisition of NDM-producing CRE; results of environmental cultures and organism typing.

RESULTS In total, 39 case patients were identified from January 2013 through December 2013, 35 with duodenoscope exposure in 1 hospital. No lapses in duodenoscope reprocessing were identified; however, NDM-producing *Escherichia coli* was recovered from a reprocessed duodenoscope and shared more than 92% similarity to all case patient isolates by PFGE. Based on the case-control study, case patients had significantly higher odds of being exposed to a duodenoscope (odds ratio [OR], 78 [95% CI, 6.0-1008], $P < .001$). After the hospital changed its reprocessing procedure from automated high-level disinfection with ortho-phthalaldehyde to gas sterilization with ethylene oxide, no additional case patients were identified.

CONCLUSIONS AND RELEVANCE In this investigation, exposure to duodenoscopes with bacterial contamination was associated with apparent transmission of NDM-producing *E coli* among patients at 1 hospital. Bacterial contamination of duodenoscopes appeared to persist despite the absence of recognized reprocessing lapses. Facilities should be aware of the potential for transmission of bacteria including antimicrobial-resistant organisms via this route and should conduct regular reviews of their duodenoscope reprocessing procedures to ensure optimal manual cleaning and disinfection.

Author Affiliations: Author affiliations are listed at the end of this article.

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JAMA. 2014;312(14):1447-1455. doi:10.1001/jama.2014.12720

CRE Transmission via ERCP Scopes

- A US Senate investigation found 250 scope-related CRE infections reported from 25 hospitals/clinics in the US and Europe, 2012-2015

Promed-mail, Apr. 16, 2016

Carbapenemase-Producing *Enterobacteriaceae*

- KPC (*Klebsiella pneumoniae* carbapenemase)
- NDM-1 (New Delhi metallo-β-lactamase)

KPC

- *K. pneumoniae* carbapenemase (Ambler class A serine β-lactamase)
- bla_{KPC} gene resides on a transposon, Tn4401
- hydrolyzes all β-lactams, and typically multidrug-resistant

K. pneumoniae Carbapenemase

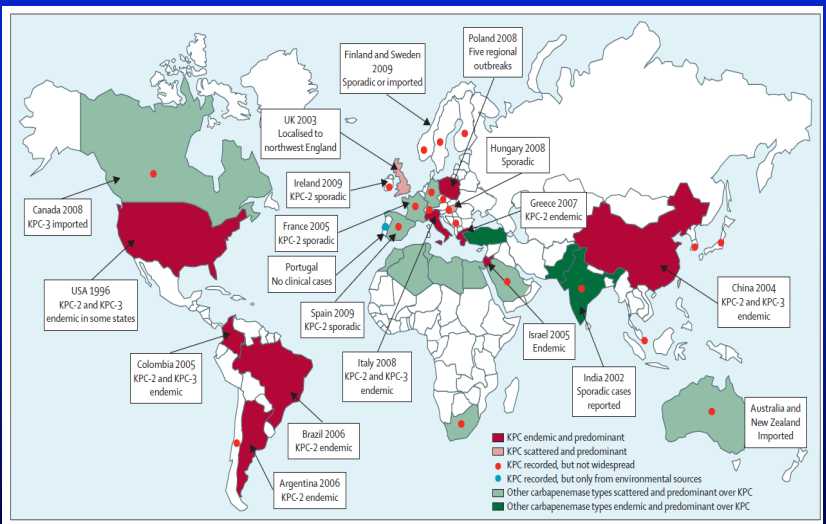


Figure: Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin
Other carbapenemase types include VIM, OXA-48, or NDM. KPC=*Klebsiella pneumoniae* carbapenemase.

Munoz-Price, Lancet Infect Dis 2013

KPC - Epidemiology

- clonal outbreaks in New York, Israel, Greece, Colombia, Brazil, China
- outbreaks in Montreal and Toronto hospitals

KPC in the US

- KPC is the most common carbapenemase in the US, and is endemic in many areas
- NYC: 2% of ICU patients colonized or infected with KPC, and KPC accounted for 26% of all invasive *K. pneumoniae* infections
- Chicago: 3% of ICU patients and 30% of LTACH residents

Calfee, Infect Control Hosp Epidemiol 2008; Patel, Infect Control Hosp Epidemiol 2008; Lin, Clin Infect Dis 2013

KPC in the US

- meropenem-resist *K. pneumoniae* increased from 0.6% in 2004 to 5.6% in 2008[1]
- NHSN surveillance of device-related infections (2006-07): carbapenem-resist in 10.8% *K. pneumoniae* and 4.0% *E. coli* [2]

[1]Rhomberg, Diagn Microbiol Infect Dis 2009;
[2]Hidron, Infect Control Hosp Epidemiol 2008

KPC
Risk Factors

- prior use of multiple antibiotics, especially a β-lactam or fluoroquinolone
- prolonged hospitalization
- ICU admission

Woodward, Antimicrob Agents Chemother 2004; Bratu, Arch Intern Med 2005; Nordmann, Lancet Infect Dis 2009

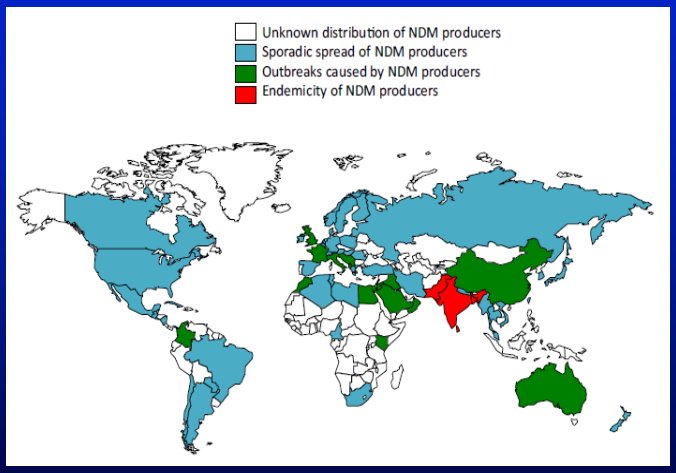
KPC Outcome

- KPC infection associated with higher mortality than that caused by carbapenem-susceptible organism
  (Bratu, Arch Intern Med 2005; Marchaim, Antimicrob Agents Chemother 2008)
- KPC BSI associated with 40%-70% crude mortality, and attributable mortality as high as 50%
  (Schwaber, Antimicrob Agents Chemother 2008; Borer, Infect Control Hosp Epidemiol 2009; Ben-David, Clin Microbiol Infect 2012; Tumbarello, Clin Infect Dis 2012)

NDM-1

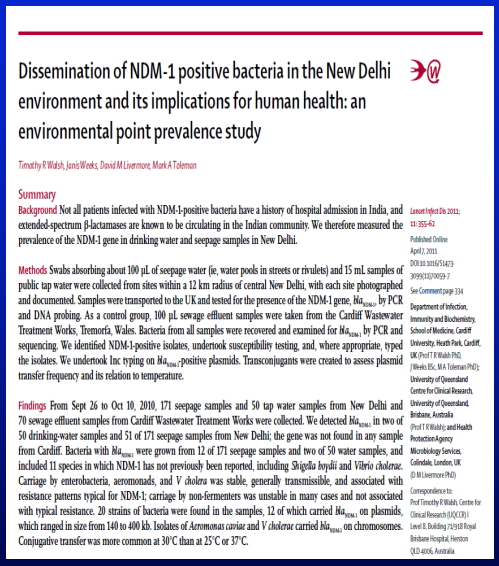
- New Delhi metallo-β-lactamase
- plasmid-mediated
- has been found in many different coliform species
- resistant to all β-lactams and to most other classes of antibiotics

NDM-1



Endemic in south Asia

Kumarasamy, Lancet Infect Dis 2010;
Nordmann, Clin Microbiol Infect 2014



Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Toleman

Summary

Background Not all patients infected with NDM-1-positive bacteria have a history of hospital admission in India, and extended-spectrum β-lactamases are known to be circulating in the Indian community. We therefore measured the prevalence of the NDM-1 gene in drinking water and seepage samples in New Delhi.

Methods Swabs absorbing about 100 µL of seepage water (ie, water pools in streets or rivulets) and 15 mL samples of public tap water were collected from sites within a 12 km radius of central New Delhi, with each site photographed and documented. Samples were transported to the UK and tested for the presence of the NDM-1 gene, bla_{NDM-1}, by PCR and DNA probing. As a control group, 100 µL sewage effluent samples were taken from the Cardiff Wastewater Treatment Works, Tremorfa, Wales. Bacteria from all samples were recovered and examined for bla_{NDM-1} by PCR and sequencing. We identified NDM-1-positive isolates, undertook susceptibility testing, and, where appropriate, typed the isolates. We undertook Inc typing on bla_{NDM-1}-positive plasmids. Transconjugants were created to assess plasmid transfer frequency and its relation to temperature.

Findings From Sept 26 to Oct 10, 2010, 171 seepage samples and 50 tap water samples from New Delhi and 70 sewage effluent samples from Cardiff Wastewater Treatment Works were collected. We detected bla_{NDM-1} in two of 50 drinking-water samples and 51 of 171 seepage samples from New Delhi; the gene was not found in any sample from Cardiff. Bacteria with bla_{NDM-1} were grown from 12 of 171 seepage samples and two of 50 water samples, and included 11 species in which NDM-1 has not previously been reported, including *Shigella boydii* and *Vibrio cholerae*. Carriage by enterobacteria, aeromonads, and *V cholera* was stable, generally transmissible, and associated with resistance patterns typical for NDM-1; carriage by non-fermenters was unstable in many cases and not associated with typical resistance. 20 strains of bacteria were found in the samples, 12 of which carried bla_{NDM-1} on plasmids, which ranged in size from 140 to 400 kb. Isolates of *Aeromonas caviae* and *V cholerae* carried bla_{NDM-1} on chromosomes. Conjugative transfer was more common at 30°C than at 25°C or 37°C.

Lancet Infect Dis 2011; 11: 355–62
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See Comment page 334

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- **NDM-1 widespread in tap water and sewage in New Delhi, India**
- **2/50 water specimens and 12/170 sewage specimens**
- **20 different bacterial species**

(can also be found in surface water and sewage in Canada)

Walsh, Lancet Infect Dis 2011

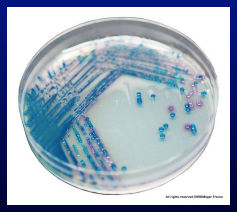
NDM-1 Outcome

- In a case–control study of patients with hospital-acquired NDM-1 infection, adjusting for co-morbidity, NDM-1 infected patients had:
  - longer mean LOS (44 vs. 13 days; p<0.001)
  - higher mortality (55% vs. 15%; aOR 11.3)

De Jager, PLoS One 2015

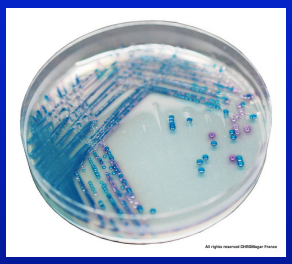
Carbapenem Resistance Diagnosis/Detection

- Lab detection challenging due to heterogeneous expression of resistance to β-lactams

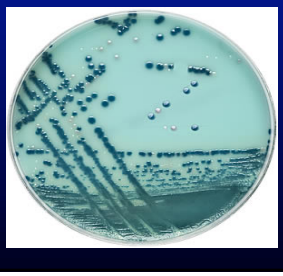


Chromogenic Media

KPC Chromagar (Colorex)



Brilliance CRE



- KPC Chromagar for KPC detection:
  100% sensitive
  98% specific
- less sensitive for other carbapenemases

Perry, J Antimicrob Chemother 2011;
Wilkinson, J Clin Microbiol 2012;
Simner, J Clin Microbiol 2016

Tests for Carbapenemases

- Phenotypic tests
  - Modified Hodge Test (MHT)
  - Carba NP
  - Carbapenem Inactivation Method
- Molecular tests
  - PCR

PCR for CPE Screening from Rectal Swabs

Journal of Hospital Infection 88 (2014) 66–71
Available online at www.sciencedirect.com
Journal of Hospital Infection
journal homepage: www.elsevierhealth.com/journals/jhin

Routine active surveillance for carbapenemase-producing Enterobacteriaceae from rectal swabs: diagnostic implications of multiplex polymerase chain reaction

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J Antimicrob Chemother 2015; 70: 1669–1673
doi:10.1093/jac/dkv009 Advance Access publication 29 January 2015
Journal of Antimicrobial Chemotherapy

Multicentre evaluation of the Check-Direct CPE® assay for direct screening of carbapenemase-producing Enterobacteriaceae from rectal swabs

Te-Din Huang[1]*, Pierre Bogaerts[1], Enes Ghilani[1], Amélie Heinrichs[1], Pierre Gavage[2], Sandrine Roisin[3], Elise Willems[4], Anne-Marie Verbruggen[4], Hugo Francart[4], Olivier Denis[5], Jean-Marc Senterre[2] and Youri Glupczynski[1]
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GeneXpert Carba-R
- *bla*$_{KPC}$
- *bla*$_{NDM}$
- *bla*$_{VIM}$
- *bla*$_{OXA-48}$
- *bla*$_{IMP}$

CPE Challenges

- **multiresistant** (few treatment options)
- **lab detection may be difficult** (screening media; confirmation of CPE)
- **prolonged fecal carriage and easily transmitted** (clonal spread or plasmids)
- **environmental contamination may be common, unrecognized** (sinks, endoscopes)
- **lack of data re: effective infection control**

KPC & NDM-1 Outbreaks Controlled with 'bundles':

- attention to hand hygiene
- active screening
- contact precautions
- cohorting as required
- enhanced environmental cleaning
- antibiotic stewardship

Kochar, Infect Control Hosp Epidemiol 2009; Borgia, Clin Infect Dis 2012; Lowe, Infect Control Hosp Epidemiol 2013; Fournier, Euro Surveill 2014; Abdallah, J Antimicrob Chemother 2016

CPE Infection Control Guidelines

TABLE 2. Comparison of the Recommendations Made by Different Authorities Regarding Infection Prevention and Control of Carbapenemase-Producing *Enterobacteriaceae* (CPE)

Recommendations	CDC[49,60]	HPA[43]	PHAC CINQ[45,47]	EU[48]	FR[43]
Facility/institution engagement					
Ensure that the board and executives make CPE prevention a high priority and are supportive/include all healthcare facilities/providers	R	R	...	...	...
Prepare a containment action plan	...	R	...	...	...
Isolation of patients					
Use preemptive contact precautions for patients transferred from endemic areas	S	R	R	...	R
Use contact precautions for patients colonized with CPE	R	R	R	R	R
Use contact precautions for patients infected with CPE	R	R	R	R	R
Use contact precautions for patients hospitalized in the same environment/room as a positive case while cultures are pending	S	...	R	...	...
Use contact precautions for epidemiologically linked patients while surveillance cultures are pending	S	...	...	...	...
Duration of isolation					
Maintain for the entire length of stay	...	...	R	R	...

R, Recommended; S, Suggested

Savard, Infect Control Hosp Epidemiol 2013

CPE Infection Control Guidelines

Surveillance					
Screen high-risk patients on admission (known positives and those returning from endemic areas if hospitalized)	R	R	R	R	R
Perform point prevalence survey on high-risk units	R	...	R	...	...
Conduct a round of active surveillance cultures on epidemiologically linked patients (same unit/same healthcare workers)	R	R	R	R	R
Repeated surveillance cultures					
Repeat surveillance cultures if patient-to-patient transmission occurred	R	R	R	R	...
Screen household contacts of patients	...	S	...	...	...
Follow surveillance cultures to determine whether colonization persists	S	...	...	...	R
Other infection prevention/control measures					
Enhance/monitor infection control measures	R	R	R	R	R
Add droplet precautions if respiratory tract is colonized/infected	...	...	...	...	R
Cohort patients if necessary	R	R	...	R	R
Flag patient record	R	R	R	R	R
Implement antimicrobial stewardship program	R	R	R	R	R
Limit use of devices	R	...	...	...	...
Environment cleaning					
Use same disinfection process as for MRSA	...	...	R	...	...
Consider increased frequency of cleaning and use of disinfectant	...	R	...	S	...

Savard, Infect Control Hosp Epidemiol 2013

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*

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

Background. During 2006, Israeli hospitals faced a clonal outbreak of carbapenem-resistant *Klebsiella pneumoniae* that was not controlled by local measures. A nationwide intervention was launched to contain the outbreak and to introduce a strategy to control future dissemination of antibiotic-resistant bacteria in hospitals.

Methods. In March 2007, the Ministry of Health issued guidelines mandating physical separation of hospitalized carriers of carbapenem-resistant Enterobacteriaceae (CRE) and dedicated staffing and appointed a professional task force charged with containment. The task force paid site visits at acute-care hospitals, evaluated infection-control policies and laboratory methods, supervised adherence to the guidelines via daily census reports on carriers and their conditions of isolation, provided daily feedback on performance to hospital directors, and intervened additionally when necessary. The initial intervention period was 1 April 2007–31 May 2008. The primary outcome measure was incidence of clinically diagnosed nosocomial CRE cases.

Results. By 31 March 2007, 1275 patients were affected in 27 hospitals (175 cases per 1 million population). Prior to the intervention, the monthly incidence of nosocomial CRE was 55.5 cases per 100,000 patient-days. With the intervention, the continuous increase in the incidence of CRE acquisition was halted, and by May 2008, the number of new monthly cases was reduced to 11.7 cases per 100,000 patient-days ($P < .001$). There was a direct correlation between compliance with isolation guidelines and success in containment of transmission ($P = .02$). Compliance neutralized the effect of carrier prevalence on new incidence ($P = .03$).

Conclusions. A centrally coordinated intervention succeeded in containing a nationwide CRE outbreak after local measures failed. The intervention demonstrates the importance of strategic planning and national oversight in combating antimicrobial resistance.

Nation-wide Control of KPCs in Israel

Schwaber, Clin Infect Dis 2011

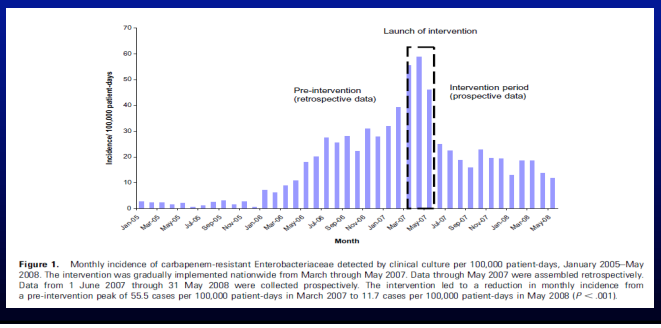


Figure 1. Monthly incidence of carbapenem-resistant Enterobacteriaceae detected by clinical culture per 100,000 patient-days, January 2005–May 2008. The intervention was gradually implemented nationwide from March through May 2007. Data through May 2007 were assembled retrospectively. Data from 1 June 2007 through 31 May 2008 were collected prospectively. The intervention led to a reduction in monthly incidence from a pre-intervention peak of 55.5 cases per 100,000 patient-days in March 2007 to 11.7 cases per 100,000 patient-days in May 2008 ($P < .001$).

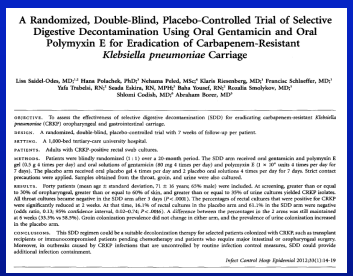
KPC Control in Israel

Nationally mandated IP&C "bundle" implem in 2007-2008:

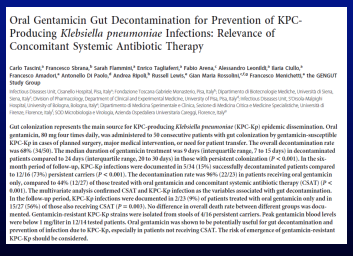
- active surveillance (rectal swab) for all high-risk patients
- contact precautions in private room or cohorting of all CRE patients; cohorting staff and dedicated equipment
- flag patients on readmission
- mandatory reporting to public health of every CRE patient, and daily census
- national task force to oversee, provide feedback, and advice to individual hospitals

Cohen, ICHE 2011; Borer, ICHE 2011; Schwaber, CID 2011; Schwaber, CID 2014

KPC Decolonization



A Randomized, Double-Blind, Placebo-Controlled Trial of Selective Digestive Decontamination Using Oral Gentamicin and Oral Polymyxin E for Eradication of Carbapenem-Resistant *Klebsiella pneumoniae* Carriage



Oral Gentamicin Gut Decontamination for Prevention of KPC-Producing *Klebsiella pneumoniae* Infections: Relevance of Concomitant Systemic Antibiotic Therapy

- RTC: oral gentamicin + polymyxin E vs. placebo X 7 days
- ↓ KPC rectal carriage for up to 6 weeks

- case series, 50 patients
- oral gentamicin
- ↓ KPC colonization
- ↓ KPC infections

Colistin

INVITED ARTICLE | REVIEWS OF ANTI-INFECTIVE AGENTS

Louis D. Saravolatz, Section Editor

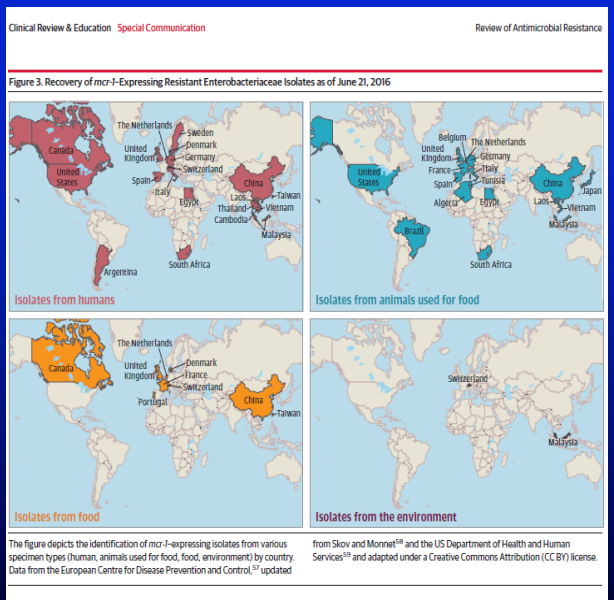
Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections

Matthew E. Falagas[1,2,3] and Sofia K. Kasiakou[1]

[1]Alfa Institute of Biomedical Sciences (AIBS) and [2]Department of Medicine, "Henry Dunant" Hospital, Athens, Greece; and [3]Tufts University School of Medicine, Boston, Massachusetts

The emergence of multidrug-resistant gram-negative bacteria and the lack of new antibiotics to combat them have led to the revival of polymyxins, an old class of cationic, cyclic polypeptide antibiotics. Polymyxin B and polymyxin E (colistin) are the 2 polymyxins used in clinical practice. Most of the reintroduction of polymyxins during the last few years is related to colistin. The polymyxins are active against selected gram-negative bacteria, including *Acinetobacter* species, *Pseudomonas aeruginosa*, *Klebsiella* species, and *Enterobacter* species. These drugs have been used extensively worldwide for decades for local use. However, parenteral use of these drugs was abandoned ~20 years ago in most countries, except for treatment of patients with cystic fibrosis, because of reports of common and serious nephrotoxicity and neurotoxicity. Recent studies of patients who received intravenous polymyxins for the treatment of serious *P. aeruginosa* and *Acinetobacter baumannii* infections of various types, including pneumonia, bacteremia, and urinary tract infections, have led to the conclusion that these antibiotics have acceptable effectiveness and considerably less toxicity than was reported in old studies.

Falagas, Clin Infect Dis 2005



Colistin-Resistant Enterobacteriaceae

Marston, JAMA 2016

mcr-1-positive Colistin-Resistance in Canada

- A few reports of *mcr* resistance in human isolates reported as of Mar. 2017:

Mulvey, Lancet Infect Dis 2016;
Payne, Emerg Infect Dis 2016;
Walkty, CMAJ Open 2016

Summary

- Although still uncommon in Canadian hospitals, the incidence of CPEs is rising, including increased rates of nosocomial transmission
- Enormous impact on patient mortality and outcome
- IP&C and antimicrobial stewardship are critical to reduce emergence and spread

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