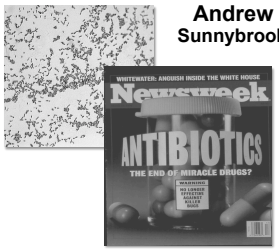
Emerging Carbapenem Resistance – What Do We Do Now?

Prof. Andrew Simor, University of Toronto
A Webber Training Teleclass

Emerging Carbapenem Resistance: What Do We Do Now?



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

Hosted by Paul Webber
paul@webbertraining.com

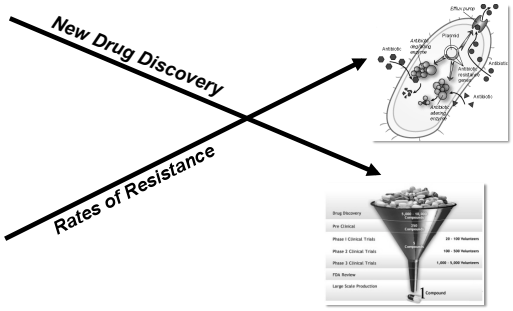
Disclosures

I have no disclosures or conflicts of interest to declare.

Objectives

- **to understand the epidemiology, risks, and impact of carbapenem-resistant organisms in hospitals**
- **to consider effective strategies for preventing the emergence and spread of carbapenem resistance in healthcare settings**

We Have a Basic Problem

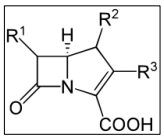


Carbapenems "The Big Gun"

- **ertapenem**
- **imipenem**
- **meropenem**
- **doripenem**

Carbapenems

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



Hosted by Paul Webber paul@webbertraining.com
www.webbertraining.com

Emerging Carbapenem Resistance – What Do We Do Now?

Prof. Andrew Simor, University of Toronto

A Webber Training Teleclass

Carbapenems – Common Indications

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

Carbapenem Resistance

- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.
- *Enterobacteriaceae* (eg. *Klebsiella, E. coli*)

Carbapenem Resistance

- changes in OMPs (permeability barrier: porin loss + ESBL/AmpC ß-lactamase); especially in *Pseudomonas*
- carbapenemases:
  - class A (serine)
  - class B (metallo-ß-lactamase)
  - class D (OXA ß-lactamase)

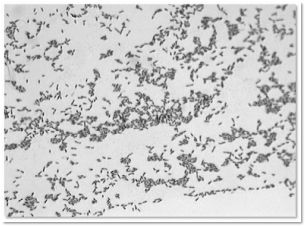
Carbapenemases

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*)

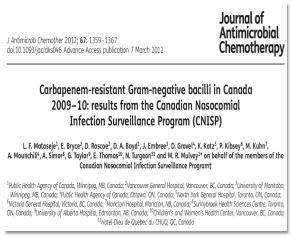
Carbapenem Resistance in Gram-Negative Bacilli:



How Common Is This?

Carbapenem-Resistant GNB in Canadian Hospitals (1)

- 1-yr surveillance in 20 hospitals, 2009-2010
- 58,669 GNB
  6,260 *P. aeruginosa*
  331 *A. baumannii*
  52,078 coliforms
  34,182 *E. coli*
  7,363 *Klebsiella*



J Antimicrob Chemother 2012; 67: 1359–1367
doi:10.1093/jac/dks046 Advance Access publication 7 March 2012

Journal of Antimicrobial Chemotherapy

Carbapenem-resistant Gram-negative bacilli in Canada 2009–10: results from the Canadian Nosocomial Infection Surveillance Program (CNISP)

L. F. Mataseje[1], E. Bryce[2], D. Roscoe[2], D. A. Boyd[1], J. Embree[3], D. Gravel[4], K. Katz[5], P. Kibsey[6], M. Kuhn[7], A. Mounchili[8], A. Simor[9], G. Taylor[8], E. Thomas[10], N. Turgeon[11] and M. R. Mulvey[1]* on behalf of the members of the Canadian Nosocomial Infection Surveillance Program†

[1]Public Health Agency of Canada, Winnipeg, MB, Canada; [2]Vancouver General Hospital, Vancouver, BC, Canada; [3]University of Manitoba, Winnipeg, MB, Canada; [4]Public Health Agency of Canada, Ottawa, ON, Canada; [5]North York General Hospital, Toronto, ON, Canada; [6]Victoria General Hospital, Victoria, BC, Canada; [7]Moncton Hospital, Moncton, NB, Canada; [8]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [9]University of Alberta Hospital, Edmonton, AB, Canada; [10]Children's and Women's Health Center, Vancouver, BC, Canada; [11]Hotel-Dieu de Quebec du CHUQ, QC, Canada

Mataseje, J Antimicrob Chemother 2012

Emerging Carbapenem Resistance – What Do We Do Now?

Prof. Andrew Simor, University of Toronto

A Webber Training Teleclass

Carbapenem-Resistant GNB in Canadian Hospitals (2)

P. aeruginosa

206 (3.3%) carbapenem-resistant; only 11 (5%) had a carbapenemase (*bla*$_{VIM}$ in 8; *bla*$_{GES}$ in 3)

A. baumannii

9 (2.7%) carbapenem-resistant; all *bla*$_{OXA}$

Mataseje, J Antimicrob Chemother 2012

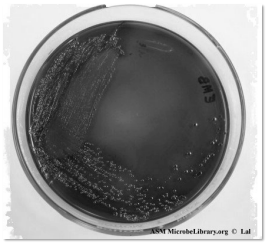
Carbapenem-Resistant GNB in Canadian Hospitals (3)

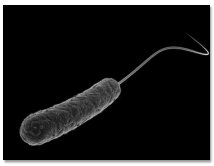
Enterobacteriaceae

59 (0.1%) carbapenem-resistant:
10 (17%) with carbapenemase KPC (7), NDM-1 (2), SME (1), 6 *Klebsiella*, 2 *E. coli*, 2 *Serratia*

Mataseje, J Antimicrob Chemother 2012

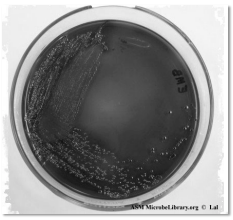
Carbapenem-Resistant *Pseudomonas*





Pseudomonas aeruginosa

- **2nd most common isolate in US ICUs[1]**
- **3rd most common isolate in Canadian ICUs and Canadian wards[2,3]**

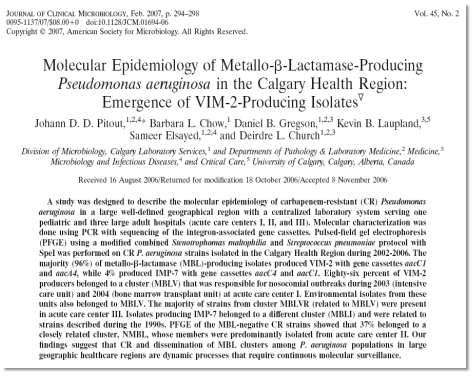


[1]Streit, J Antimicrob Chemother 2004; [2] Zhanel, Antimicrob Agents Chemother 2008; [3] McCracken, Diagn Microbiol Infect Dis 2011

Carbapenem-Resistant *P. aeruginosa*

- **carbapenem resistance mostly due to: efflux, altered outer membrane proteins (loss of OprD), or increased AmpC expression[1,2]**
- **less often due to a carbapenemase, esp. VIM, less often IMP, NDM-1[3]**

[1]Davies, J Antimicrob Chemother 2011; [2]Rodriguez-Martinez, Antimicrob Agents Chemother 2009; [3]Libisch, Antimicrob Agents Chemother 2004



JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2007, p. 294–298 Vol. 45, No. 2
0095-1137/07/$08.00+0 doi:10.1128/JCM.01694-06
Copyright © 2007, American Society for Microbiology. All Rights Reserved.

Molecular Epidemiology of Metallo-β-Lactamase-Producing *Pseudomonas aeruginosa* in the Calgary Health Region: Emergence of VIM-2-Producing Isolates[▽]

Johann D. D. Pitout,[1,2,4]* Barbara L. Chow,[1] Daniel B. Gregson,[1,2,3] Kevin B. Laupland,[3,5] Sameer Elsayed,[1,2,4] and Deirdre L. Church[1,2,3]

Division of Microbiology, Calgary Laboratory Services,[1] and Departments of Pathology & Laboratory Medicine,[2] Medicine,[3] Microbiology and Infectious Diseases,[4] and Critical Care,[5] University of Calgary, Calgary, Alberta, Canada

Received 16 August 2006/Returned for modification 18 October 2006/Accepted 8 November 2006

A study was designed to describe the molecular epidemiology of carbapenem-resistant (CR) *Pseudomonas aeruginosa* in a large well-defined geographical region with a centralized laboratory system serving one pediatric and three large adult hospitals (acute care centers I, II, and III). Molecular characterization was done using PCR with sequencing of the integron-associated gene cassettes. Pulsed-field gel electrophoresis (PFGE) using a modified combined *Stenotrophomas maltophilia* and *Streptococcus pneumoniae* protocol with SpeI was performed on CR *P. aeruginosa* strains isolated in the Calgary Health Region during 2002-2006. The majority (96%) of metallo-β-lactamase (MBL)-producing isolates produced VIM-2 with gene cassettes *aacC1* and *aac44*, while 4% produced IMP-7 with gene cassettes *aacC4* and *aacC1*. Eighty-six percent of VIM-2 producers belonged to a cluster (MBLV) that was responsible for nosocomial outbreaks during 2003 (intensive care unit) and 2004 (bone marrow transplant unit) at acute care center I. Environmental isolates from these units also belonged to MBLV. The majority of strains from cluster MBLVR (related to MBLV) were present in acute care center III. Isolates producing IMP-7 belonged to a different cluster (MBLI) and were related to strains described during the 1990s. PFGE of the MBL-negative CR strains showed that 37% belonged to a closely related cluster, NMBL, whose members were predominantly isolated from acute care center II. Our findings suggest that CR and dissemination of MBL clusters among *P. aeruginosa* populations in large geographic healthcare regions are dynamic processes that require continuous molecular surveillance.

Emerging Carbapenem Resistance – What Do We Do Now?

Prof. Andrew Simor, University of Toronto

A Webber Training Teleclass

Carbapenem-Resistant *Pseudomonas*: Risk Factors

- **ICU admission** (Harris, Clin Infect Dis 2002; Eagye, Infect Control Hosp Epidemiol 2009)
- **prior treatment with a carbapenem** (Troillet, Clin Infect Dis 1997; Harris, Clin Infect Dis 2002; Magno, Infect Control Hosp Epidemiol 2006)
- **prior treatment with other antibiotics (fluoroquinolones, Vanco, pip/tazo)** (Harris, Clin Infect Dis 2002; Lautenbach, Infect Control Hosp Epidemiol 2006)

Carbapenem-Resistant *Pseudomonas* - Sunnybrook

- **increased from 4.1% in 2002 to 15% in 2010** (p=0.001); **80% in ICU**
- **risk factors: prior carbapenem** (OR 6.2, 95% CI 2.1-18.8), **fluoroquinolone** (OR 2.7, 95% CI 1.2-6.1), **ICU admission** (OR 2.9, 95% CI 1.3-6.7)
- **multiple clones; only 3 (6%) had a carbapenemase by PCR (*bla*$_{IMP}$)**

Allen, SHEA 2009

Carbapenem-Resistant *Pseudomonas* - Sunnybrook

- **associated with increased in-hospital mortality** (26% vs 11%; p=0.01)
- **"ineffective" antibiotics initially prescribed in 24%, but not associated with increased mortality** (33% vs 22%; p=0.45)

Allen, SHEA 2009

Carbapenem-Resistant *P. aeruginosa* - Outcome

- **Carbapenem resistance in *P. aeruginosa* is a significant independent risk factor for mortality as compared to susceptible strains** (31% vs 17%; RR 1.9, 95% CI 1.4-2.5)[1]
- **Carbapenem resistance also associated with longer LOS and increased costs**[2]

[1]Lautenbach, Infect Control Hosp Epidemiol 2006;
[2]Eagye, Infect Control Hosp Epidemiol 2009

Does ertapenem use spare carbapanem resistance in *Pseudomonas*?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2009, p. 5222–5226 Vol. 53, No. 12
0066-4804/09/$12.00 doi:10.1128/AAC.00864-09
Copyright © 2009, American Society for Microbiology. All Rights Reserved.

Introduction of Ertapenem into a Hospital Formulary: Effect on Antimicrobial Usage and Improved In Vitro Susceptibility of *Pseudomonas aeruginosa*[▽]

Ellie J. C. Goldstein,[1,2]* Diane M. Citron,[1] Victoria Peraino,[3] Tanya Elgourt,[4] Anne R. Meibohm,[5] and Shuang Lu[5]

RM Alden Research Laboratory, Santa Monica, California[1]; Department of Infectious Diseases,[2] Microbiology,[3] and Pharmacy,[4] St. Johns' Health Center, Santa Monica, California 90404; and Merck & Co., Inc., North Wales, Pennsylvania[5]

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY MAY 2006, VOL. 26, NO. 5

CONCISE COMMUNICATION

The Impact of Ertapenem Use on the Susceptibility of *Pseudomonas aeruginosa* to Imipenem: A Hospital Case Study

Ana Lucia L. Lima, MD, PhD; Priscila R. Oliveira, MD; Adriana P. Prado, RN; Karine Dal-Paz, PharmD; Flavia Rossi, MD, PhD; Arnaldo V. Zoratto, MD, PhD

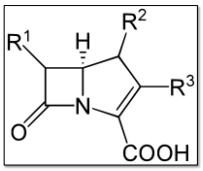
INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY MAY 2005, VOL. 26, NO. 5

ORIGINAL ARTICLE

Absence of Association between Use of Ertapenem and Change in Antipseudomonal Carbapenem Susceptibility Rates in 25 Hospitals

Kathryn J. Eagye, MPH; David P. Nicolau, PharmD, FCCP, FIDSA

Carbapenemases



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

Carbapenemases

Metallo-β-lactamase (class B)
- inhibited by EDTA
- contain a zinc atom at the active site
- NDM-1, IMI, GES, Sme

Serine β-lactamase (class A)
- not inhibited by EDTA
- serine at active site
- KPC, VIM, IMP

Class D enzymes
OXA-48 (*E. coli*, *K. pneumoniae*)

Carbapenem-Resistant *Enterobacteriaceae*

Ontario Public Health Lab (Apr. 2008 – Mar. 2012)

NDM-1	34
KPC	33
OXA-48	14
VIM	6

K. pneumoniae	54
E. coli	13
E. cloacae	9

Public Health Ontario, CPE Surveillance Report, May 2012

Carbapenem-Resistant *Enterobacteriaceae*

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

KPC

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

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

Carbapenem-Resistant *Enterobacteriaceae*

- meropenem-resist *K. pneumoniae* increased from 0.6% in 2004 to 5.6% in 2008 (in the US)[1]
- NHSN surveillance 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

Emerging Carbapenem Resistance – What Do We Do Now?

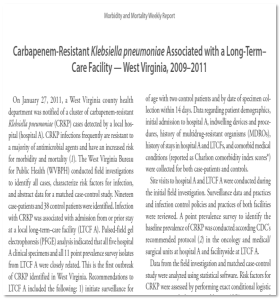
Prof. Andrew Simor, University of Toronto

A Webber Training Teleclass

Carbapenem-Resistant *Enterobacteriaceae*

- **KPC is the most common carbapenemase in the US**
- **In NYC:**
  - **2% of ICU patients colonized/infected with KPC[1]**
  - **KPC accounted for 26% of all invasive *K. pneumoniae* infections[2]**

[1]Calfee, Infect Control Hosp Epidemiol 2008;
[2]Patel, Infect Control Hosp Epidemiol 2008



Morbidity and Mortality Weekly Report

Carbapenem-Resistant *Klebsiella pneumoniae* Associated with a Long-Term-Care Facility — West Virginia, 2009–2011

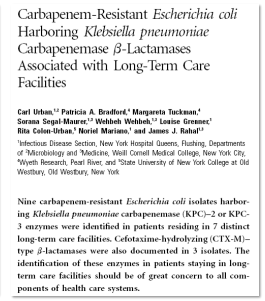
On January 27, 2011, a West Virginia county health department was notified of a cluster of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) cases detected by a local hospital (hospital A). CRKP infections frequently are resistant to a majority of antimicrobial agents and have an increased risk for morbidity and mortality (1). The West Virginia Bureau for Public Health (WVBPH) conducted field investigations to identify all cases, characterize risk factors for infection, and abstract data for a matched case-control study. Nineteen case-patients and 38 control patients were identified. Infection with CRKP was associated with admission from or prior stay at a local long-term–care facility (LTCF A). Pulsed-field gel electrophoresis (PFGE) analysis indicated that all five hospital A clinical specimens and all 11 point-prevalence survey isolates from LTCF A were closely related. This is the first outbreak of CRKP identified in West Virginia. Recommendations to LTCF A included the following: 1) initiate surveillance for

of age with two control patients and by date of specimen collection within 14 days. Data regarding patient demographics, initial admission to hospital A, indwelling devices and procedures, history of multidrug-resistant organisms (MDROs), history of stays in hospital A and LTCFs, and comorbid medical conditions (reported as Charlson comorbidity index scores*) were collected for both case-patients and controls.

Site visits to hospital A and LTCF A were conducted during the initial field investigation. Surveillance data and practices and infection control policies and practices of both facilities were reviewed. A point prevalence survey to identify the baseline prevalence of CRKP was conducted according CDC's recommended protocol (2) in the oncology and medical/surgical units at hospital A and facilitywide at LTCF A.

Data from the field investigation and matched case-control study were analyzed using statistical software. Risk factors for CRKP were assessed by performing exact conditional logistic

Clonal outbreak in a nursing home involving 19 patients; associated with indwelling urinary catheters
Gaviria, MMWR 2011



Carbapenem-Resistant *Escherichia coli* Harboring *Klebsiella pneumoniae* Carbapenemase β-Lactamases Associated with Long-Term Care Facilities

Carl Urban,[1,2] Patricia A. Bradford,[4] Margareta Tuckman,[4] Sorana Segal-Maurer,[1,3] Wehbeh Wehbeh,[1,3] Louise Grenner,[1] Rita Colon-Urban,[1] Noriel Mariano,[1] and James J. Rahal[1,3]

[1]Infectious Disease Section, New York Hospital Queens, Flushing, Departments of [2]Microbiology and [3]Medicine, Weill Cornell Medical College, New York City, [4]Wyeth Research, Pearl River, and [5]State University of New York College at Old Westbury, Old Westbury, New York

Nine carbapenem-resistant *Escherichia coli* isolates harboring *Klebsiella pneumoniae* carbapenemase (KPC)–2 or KPC-3 enzymes were identified in patients residing in 7 distinct long-term care facilities. Cefotaxime-hydrolyzing (CTX-M)–type β-lactamases were also documented in 3 isolates. The identification of these enzymes in patients staying in long-term care facilities should be of great concern to all components of health care systems.

Non-clonal spread in 7 New York LTCFs

Urban, Clin Infect Dis 2008

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; Patel, Infect Control Hosp Epidemiol 2008)

KPC, 2011

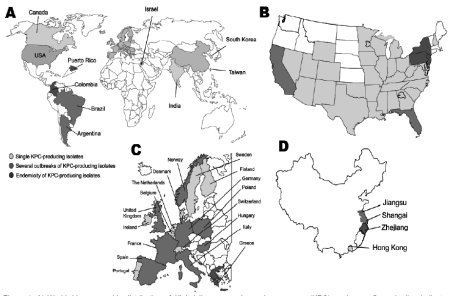


Figure 1. A) Worldwide geographic distribution of *Klebsiella pneumoniae* carbapenemase (KPC) producers. Gray shading indicates regions shown separately: B) distribution in the United States, C) distribution in Europe, D) distribution in China.

Nordmann, Emerg Infect Dis 2011

KPC - Epidemiology

- **clonal outbreaks in New York, Israel, Greece, Colombia, Brazil, China, Canada (Montreal)**

KPC Outbreak in Montreal Hospital ICU

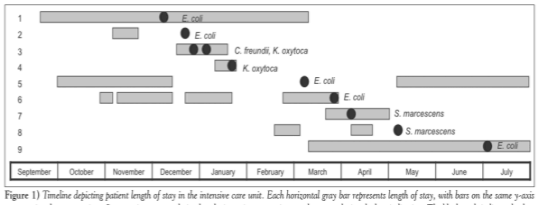


Figure 1) *Timeline depicting patient length of stay in the intensive care unit. Each horizontal gray bar represents length of stay, with bars on the same y-axis representing the same patient. Some patients were admitted to the intensive care unit more than once during the hospitalization. The black ovals indicate the date the Enterobacteriaceae isolate was obtained from the patient. Patient 3 has two isolates Citrobacter freundii and Klebsiella oxytoca. Patients 1 and 2 had Escherichia coli pulsowar A. Patients 3 and 4 had K oxytoca pulsowar D. Patient 5 had E coli pulsowar B. Patients 6 and 9 had E coli pulsowars D and D1 respectively. Patients 7 and 8 had Serratia marcescens pulsowars A*

Leung, Can J Infect Dis Med Microbiol 2012

Emerging Carbapenem Resistance – What Do We Do Now?

Prof. Andrew Simor, University of Toronto

A Webber Training Teleclass

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 (India, Pakistan, Bangladesh)
- spread to UK and other European countries; related to "medical tourism" (Kumarasamy, Lancet Infect Dis 2010)

Medical Tourism

- International travel is an important risk factor for being colonized or infected with resistant organisms (Laupland, J Infect 2008; Tängdén, Antimicrob Agents Chemother 2010)
- NDM-1 producing bacteria have been associated with admission to hospitals in south Asia (Kumarasamy, Lancet Infect Dis 2010)

NDM-1, 2011

Carbapenemase-producing *Enterobacteriaceae*

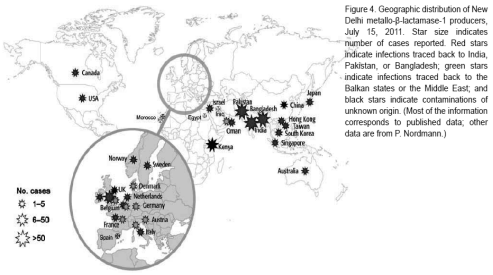


Figure 4. Geographic distribution of New Delhi metallo-β-lactamase-1 producers, July 15, 2011. Star size indicates number of cases reported. Red stars indicate infections traced back to India, Pakistan, or Bangladesh; green stars indicate infections traced back to the Balkan states or the Middle East; and black stars indicate contaminations of unknown origin. (Most of the information corresponds to published data; other data are from P. Nordmann.)

Nordmann, Emerg Infect Dis 2011

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, Donald 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 sewage samples in New Delhi.

Methods Swabs absorbing about 100 µL of sewage 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, Dumorfa, 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 S1 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 30, 2010, 171 sewage samples and 50 tap water samples from New Delhi and 76 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 sewage samples from New Delhi; the gene was not found in any sample from Cardiff. Bacteria with bla_{NDM-1} were grown from 32 of 171 sewage 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 cholerae* 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
Published Online
April 1, 2011
DOI:10.1016/S1473-3099(10)70260-7
See Comment page 324

Department of Medicine, Immunity and Biochemistry, School of Medicine, Cardiff University, Heath Park, Cardiff, UK (Prof T R Walsh PhD, J Weeks BSc, M A Toleman PhD); University of Queensland Centre for Clinical Research, University of Queensland, Brisbane, Australia (Prof T R Walsh); and Health Protection Agency Microbiology Services, Colindale, London, UK (D M Livermore PhD)

Correspondence to:
Prof Timothy R Walsh, Centre for Clinical Research (UQCCR) Level 3, Building 71/918 Royal Brisbane Hospital, Herston QLD 4029, Australia

Walsh, Lancet Infect Dis 2011

- 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

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

Hosted by Paul Webber paul@webbertraining.com

www.webbertraining.com

Emerging Carbapenem Resistance – What Do We Do Now?

Prof. Andrew Simor, University of Toronto
A Webber Training Teleclass

Carbapenem Resistance Diagnosis & Treatment

- Lab detection challenging due to heterogeneous expression of resistance to β-lactams
- Treatment options limited (tigecycline, colistin)

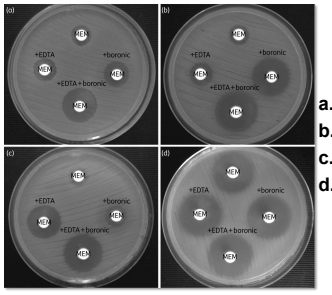
Carbapenem Resistance – Revised Breakpoints (CLSI 2010)

Carbapenem	Breakpoints (*Enterobacteriaceae*, μg/ml)		
	Susceptible	Intermediate	Resistant
Doripenem	≤ 1.0	2.0	≥ 4.0
Ertapenem	≤ 0.25	0.5	≥ 1.0
Imipenem	≤ 1.0	2.0	≥ 4.0
Meropenem	≤ 1.0	2.0	≥ 4.0

Carbapenem Resistance Lab Detection

- revised (lower) MIC breakpoints improve sensitivity of detection, but may be missed by automated systems, and may overcall carbapenemases
- disk approximation tests with inhibitors; Etest with EDTA (MBL)
- PCR

Disk Diffusion Tests for MBL and Class A (serine) Carbapenemases



a. KPC/VIM+ESBL isolate
b. KPC + ESBL isolate
c. VIM isolate
d. AmpC/ESBL isolate

Tsakris, J Antimicrob Chemother 2010

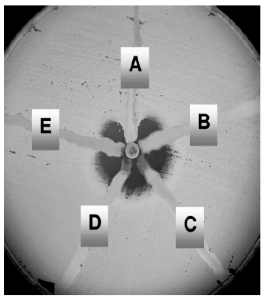
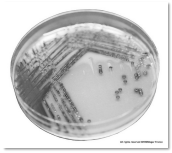


FIG. 1. The modified Hodge test Mueller-Hinton agar plate was inoculated with a 1:10 dilution of a 0.5 McFarland suspension of *E. coli* ATCC 25922 and streaked for confluent growth using a swab. A 10-μg imipenem disk was placed in the center, and each test isolate was streaked from the disk to the edge of the plate. Isolate A is a KPC producer and positive by the modified Hodge test. Isolates B, C, D, and E do not produce a carbapenemase and are negative by the test.

Modified Hodge Test

- reasonably good for KPC
- may miss NDM-1
- Nonspecific (high-level AmpC-producers)

KPC Chromagar (Colorex)



Brilliance CRE

Chromogenic Media

KPC Chromagar for KPC detection:
- 100% sensitive
- 98% specific

Samra, J Clin Microbiol 2008

Carbapenem Resistance

- emergence in a previously susceptible strain (antibiotic selective pressure)
- person-to-person transmission (clonal or plasmid)

Nosocomial Carbapenem Resistance (1)

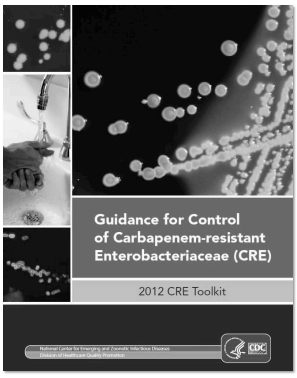
- study to determine roles of antibiotic selection pressure and patient-to-patient transmission of carbapenem-resist *P. aeruginosa*
- med/surg ICU in US, 2001-06
- serial perianal swabs on admission and weekly, to look for imipenem-resist *Pseudo* ; PFGE typing

Johnson, J Infect Dis 2009

Nosocomial Carbapenem Resistance (2)

- 7,071 patients; 300 with imipenem-resist *Pseudo* (151 on admission; 149 acquired in ICU)
- 46 (31%) had PFGE patterns suggesting transmission
- 38 (26%) had previous imipenem-susceptible *Pseudo* and 28 (19%) had same PFGE pattern, suggesting selective pressure

Johnson, J Infect Dis 2009



CDC Guidelines for Control of CRE

For all healthcare facilities
- hand hygiene
- contact precautions
- patient/staff cohorting
- contact screening
- antimicrobial stewardship

For facilities with CRE transmission
- active surveillance
- 2% chlorhexidine bathing

CDC, 2012

KPC – Infection Control

- active screening identified colonized patients who would otherwise have been missed in NYC ICUs
  (Calfee, Infect Control Hosp Epidemiol 2008)
- "bundle" (active surveillance, contact isolation, flagging, environment cleaning)
  (Ben-David, Infect Control Hosp Epidemiol 2010; Borer, Infect Control Hosp Epidemiol 2011)
- nationwide control in Israel
  (Schwaber, Clin Infect Dis 2011)

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]

[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.

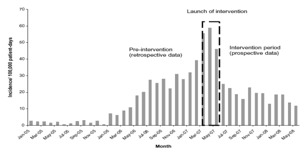


Figure 1. Monthly incidence of carbapenem-resistant Enterobacteriaceae detected by clinical culture per 100,000 patient-days, January 2005–May 2008. The intervention was gradually implemented nationwide from March through May 2007. Data through May 2007 were assembled retrospectively. Data from 1 June 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 ($P < .001$).

Schwaber, Clin Infect Dis 2011

Carbapenem Resistance Challenges in Management

- easy plasmid transmission (NDM-1)
- environmental contamination may be common, unrecognized
- lack of good screening media
- difficult algorithms for detecting or confirming resistance
- few treatment options
- lack of data re: effective infection control

Coming Soon

02 October *(FREE … WHO Teleclass – Europe)* **The Role of Education in Low and Middle Income Countries**
Speaker: Prof. Shaheen Mehtar, Stellenbosch University, South Africa
Sponsored by WHO First Global Patient Safety Challenge – Clean Care is Safer Care

11 October **Evaluating Chlorhexidine Baths for the Prevention of Central Line Associated Bloodstream Infections (CLABSIs)**
Speaker: Prof. Silvia Munoz-Price, University of Miami Miller School of Medicine
Sponsored by Sage Products Inc (www.sageproducts.com)

18 October *(South Pacific Teleclass)* **Meningococcal Disease and the New Zealand Experience – Where to From Here**
Speaker: Dr. Tony Walls, University of Otago, New Zealand

25 October **Critique and Use of the Scientific Evidence – Sharpening Skills**
Speaker: Russell Olmstead, St. Joseph Mercy Health System, Ann Arbor, Michigan
Sponsored by Virox Technologies Inc. (www.virox.com)

www.webbertraining.com/schedulep1.php