CRE Epidemiology: Global & Israeli Perspectives

Dror Marchaim, M.D.
Infection Control and Prevention
Unit of Infectious Diseases
Assaf Harofeh Medical Center
β-lactam Antibiotics
Mechanism of Action

• Inhibition of bacterial cell wall synthesis
  – Inhibition of the transpeptidation reaction of the peptidoglycan synthesis
Mechanisms of β-lactam Resistance

• **β-lactamases hydrolysis / destruction**

• Low affinity binding to PBP’s
  – Naturally occurring (*Enterococcus*)
  – Multiple mutations (*Pneumococcus*)

• Failure to penetrate to PBP target
  – ↓ penetration (loss of porins)
  – ↑ Efflux
β-lactamases Spectrum

>2000

- Penicillinase
- Broad spectrum
- Extended spectrum
- Carbapenemases
<table>
<thead>
<tr>
<th>Class</th>
<th>Spectrum</th>
<th>Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (serine)</td>
<td>Penicillinases</td>
<td>All penicillins, narrow-spectrum cephalosporins</td>
</tr>
<tr>
<td></td>
<td>Broad-spectrum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extended-spectrum</td>
<td>Broad-spectrum + oxymino + aztreonam</td>
</tr>
<tr>
<td></td>
<td>(ESBL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carbapenemases</td>
<td>Extended-spectrum + cephemycins + carbapenems</td>
</tr>
<tr>
<td>B (Metallo-β-</td>
<td>Carbapenemases</td>
<td>Extended-spectrum + cephemycins + carbapenems</td>
</tr>
<tr>
<td>lactamases, Zn2+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C (serine)</td>
<td>Cephalosporinases</td>
<td>Extended-spectrum + cephemycins</td>
</tr>
<tr>
<td>D (Serine)</td>
<td>Oxacillinases</td>
<td>All penicillins, narrow-spectrum cephalosporins</td>
</tr>
<tr>
<td></td>
<td>Broad-spectrum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extended-spectrum</td>
<td>Broad-spectrum + oxymino + aztreonam</td>
</tr>
<tr>
<td></td>
<td>Carbapenemases</td>
<td>Extended-spectrum + cephemycins + carbapenems</td>
</tr>
</tbody>
</table>
Ambler Classification of β-lactamases

- **Class A**: TEM, SHV, CTX-M, KPC
- **Class B**: NDM-1, VIM, IMP
- **Class C**: AmpC, CYM
- **Class D**: OXA
Evolution of the distribution of resistance mechanisms of carbapenemase-producing *Enterobacteriaceae* isolates, National Reference Centre, Belgium, January 2007–April 2011 (n=44)

Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

HESNA YIGIT,1 ANNE MARIE QUEENAN,2 GREGORY J. ANDERSON,1 ANTONIO DOMENECH-SANCHEZ,3 JAMES W. BIDDLE,1 CHRISTINE D. STEWARD,1 SEBASTIAN ALBERTI,4 KAREN BUSH,2 AND FRED C. TENOVER1*

Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 303331; The R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 088692; and Unidad de Investigacion, Hospital Son Dureta, Andrea Doria, Palma de Mallorca, 07014,4 and Área de Microbiología, Universidad de las Islas Baleares, Crta. Valldemosa, Palma de Mallorca, 07071,3 Spain

Received 19 September 2000/Returned for modification 21 November 2000/Accepted 23 January 2001

A *Klebsiella pneumoniae* isolate showing moderate to high-level imipenem and meropenem resistance was investigated. The MICs of both drugs were 16 μg/ml. The β-lactamase activity against imipenem and meropenem was inhibited in the presence of clavulanic acid. The strain was also resistant to extended-spectrum cephalosporins and aztreonam. Isoelectric focusing studies demonstrated three β-lactamasises, with pIs of 7.2 (SHV-29), 6.7 (KPC-1), and 5.4 (TEM-1). The presence of *bla*SHV and *bla*TEM genes was confirmed by specific PCRs and DNA sequence analysis. Transformation and conjugation studies with *Escherichia coli* showed that the β-lactamase with a pI of 6.7, KPC-1 (*K. pneumoniae* carbapenemase-1), was encoded on an approximately 50-kb nonconjugative plasmid. The gene, *bla*KPC-1, was cloned in *E. coli* and shown to confer resistance to imipenem, meropenem, extended-spectrum cephalosporins, and aztreonam. The amino acid sequence of the novel carbapenem-hydrolyzing β-lactamase, KPC-1, showed 45% identity to the pI 9.7 carbapenem-hydrolyzing β-lactamase, Sme-1, from *Serratia marcescens* S6. Hydrolysis studies showed that purified KPC-1 hydrolyzed not only carbapenems but also penicillins, cephalosporins, and monobactams. KPC-1 had the highest affinity...
Emergence of Carbapenem-Resistant *Klebsiella* Species Possessing the Class A Carbapenem-Hydrolyzing KPC-2 and Inhibitor-Resistant TEM-30 β-Lactamases in New York City

Patricia A. Bradford, Simona Bratu, Carl Urban, Melissa Visalli, Noriel Mariano, David Landman, James J. Rehal, Steven Brooks, Sandra Cebulak, and John Quade

*Wyeth Research, Pearl River, NY; State University of New York–Downstate and Kingsbrook Jewish Medical Center, Brooklyn, and Hospital Queens, Flushing, New York.*

Nineteen isolates of carbapenem-resistant *Klebsiella* species were recovered from 7 hospitals in New York City. Most *K. pneumoniae* belonged to a single ribotype. Nucleotide sequencing identified KPC-2, a chromosomally-encoded hydrolyzing β-lactamase. In 3 strains, TEM-30, an inhibitor-resistant β-lactamase, was detected. Carbapenem-resistant *Klebsiella* species possessing KPC-2 are endemic in New York City. This study documented the dissemination of an inhibitor-resistant TEM β-lactamase in the United States.

Emergence of serine carbapenemases (KPC and SME) among clinical strains of Enterobacteriaceae isolated in the United States Medical Centers: Report from the MYSTIC Program (1999–2005)

Lalitagauri M. Deshpande, Paul R. Rhomberg, Helio S. Sader, Ronald N. Jones

*JMI Laboratories, North Liberty, Iowa, USA; Universidade Federal de Sao Paulo, Sao Paulo, Brazil; Tufts University School of Medicine, Boston, Massachusetts, USA.*

Received 6 June 2006; accepted 17 July 2006

Abstract

Among 885 Enterobacteriaceae tested in the 1999 to 2005 period as part of the USA Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program, 51 strains with increased imipenem and meropenem MIC values (≥2 μg/mL) were detected. blaKPC was

Emergence of KPC-Possessing *Klebsiella pneumoniae* in Brooklyn, New York: Epidemiology and Recommendations for Detection

Simona Bratu, Mohamad Mooy, Satyen Nichani, David Landman, Carl Gullans, Barbara Pettinato, Usha Karumudi, Pooja Tolaney, and John Quade

*Department of Medicine, SUNY-Downstate Medical Center, Department of Microbiology, Kings County Hospital, and Department of Pathology Services, Coney Island Hospital, Brooklyn, New York.*

Received 14 February 2005/Returned for modification 24 March 2005/Accepted 3 April 2005

Among 257 isolates of *Klebsiella pneumoniae* collected in Brooklyn, NY, 24% were found to possess *blaKPC*-Clinical microbiology laboratories that used automated broth microdilution systems reported 15% of the KPC-possessing isolates as susceptible to imipenem. The imipenem MIC was found to be markedly affected by the inoculum. For accurate detection of KPC-possessing *K. pneumoniae*, particular attention should be paid to inoculum preparation for broth-based susceptibility methods. In addition, using etrapenem or meropenem for class reporting of carbapenem susceptibility will improve detection.


Lalitagauri M. Deshpande, Ronald N. Jones, Thomas R. Fritsche, and Helio S. Sader

ABSTRACT

Influence and dissemination of Enterobacteriaceae isolates harboring carbapenemases in various geographic regions presents a significant threat to the management of nosocomial infections. Enterobacteriaceae isolates from SENTRY Antimicrobial Surveillance Program (2000–2004) demonstrating decreased susceptibility to carbapenemase-
And in Israel... 2007-2009....
First Report on a Hyperepidemic Clone of KPC-3-Producing
Klebsiella pneumoniae in Israel Genetically Related to a
Strain Causing Outbreaks in the United States

Shiri Navon-Venezia, Azita Leavitt, Mitchell J. Schwaber, J. Kamile Rasheed, Arjun Srinivasan, Jean B. Patel, Yehuda Carmeli, and the Israeli KPC Kpn Study Group†

Epidemiology Division, Tel Aviv Sourasky Medical Center, affiliated to the Sackler Faculty of Medicine, Tel Aviv, Israel, and Centers for Disease Control and Prevention, Atlanta, Georgia

Received 24 July 2008/Returned for modification 25 September 2008/Accepted 18 November 2008

A highly epidemic carbapenem-resistant clone of KPC-3-producing Klebsiella pneumoniae emerged in Israel in 2006, causing a nationwide outbreak. This clone was genetically related to outbreak strains from the United States isolated in 2000 but differed in KPC-carrying plasmids. The threat of the global spread of hyperepidemic, extensively drug-resistant bacterial strains should be recognized and confronted.
Worldwide dissemination

Control of a multi-hospital outbreak of KPC-producing *Klebsiella pneumoniae* type 2 in France, September to October 2009

Clinical and microbiological characterization of KPC-producing *Klebsiella pneumoniae* infections in Brazil

Intercontinental spread from Israel to Colombia of a KPC-3-producing *Klebsiella pneumoniae* strain

Carbapenem-non-susceptible Enterobacteriaceae in Europe: conclusions from a meeting of national experts

Isolation of a *Klebsiella pneumoniae* Isolate of Sequence Type 258 Producing KPC-2 Carbapenemase in Korea
International dissemination of *Klebsiella pneumoniae* carbapenemase (KPC)—producing Enterobacteriaceae.

Molecular Epidemiology of KPC-Producing Klebsiella pneumoniae Isolates in the United States: Clonal Expansion of Multilocus Sequence Type 258

Brandon Kitchel, 1* J. Kamile Rasheed, 1 Jean B. Patel, 1 Arjun Srinivasan, 1 Shiri Navon-Venezia, 2 Yehuda Carmeli, 2 Alma Brolund, 3 and Christian G. Giske 3

Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia 1; Division of Epidemiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel 2; and Clinical Microbiology L2:02, Karolinska Institutet—MTC, Karolinska University Hospital Solna, SE-17176 Stockholm, Sweden 3

Received 28 January 2009/Returned for modification 29 March 2009/Accepted 2 June 2009
Europe & Worldwide

Worldwide Diversity of Klebsiella pneumoniae That Produces β-Lactamase bla_{KPC-2} Gene

Gaëlle Cuzon, Thierry Naas, HaVy Truong, Maria-Virginia Villegas, Karin T. Wisell, Yehuda Carmeli, Ana. C. Gales, Shiri Navon-Venezia, John P. Quinn, and Patrice Nordmann

Emerg Infect Dis 2010; 16:1349-56
The Israeli Story

• Late 2005 – KPC-producing *K. pneumoniae* ST-258 introduced to Israeli hospitals
  • 2006 – outbreak began: ~700 cases
  • 01/01/2007 - 04/30/2007: ~600 cases
  • Local attempts to contain: limited success
  • Crude mortality: ~40%
  • Attributable mortality of bacteremia: 50% (Borer et al, ICHE 2009)

• Since the start of the outbreak –
  • ~17,000 patients identified with CRE
  • Vast majority of isolates tested (>90%): ST-258

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012*
Nationwide epidemic curve prior to intervention

Acquisitions by clinical culture

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
A clonal outbreak, involving acute-care hospitals and long-term care facilities
Distribution of 1\textsuperscript{st}-time CRE clinical cultures by site of isolation

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012*
What was done?

• March 2007
  – Isolation guidelines issued
    • Geographic separation of carriers
    • Dedicated nursing staffing
  – Task force created by the Ministry of Health
    • First assignment: contain the outbreak

• Daily census of all CRE carriers in acute-care hospitals required as of May 1, 2007

*Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012
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 Group1

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

P<0.001

Launch of intervention

Pre-intervention (retrospective data)

Intervention period (prospective data)

Incidence/100,000 patient days

Month

Clinical Infectious Diseases 2011;52:848–855
Compliance with isolation guidelines shown to work

Effect of compliance on incidence: prevalence ratio
Feedback and intervention shown to make a difference

Group II: per 500 beds

Group I: per 1000 beds

Group III: per 250 beds

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
After 15 months...

Monthly incidence reduced from high of 55.5 cases/100,000 pt-days to 11.7 cases/100,000 pt-days

- 79% reduction
- \( P<0.001 \)
After 15 months...

Monthly incidence reduced from high of 55.5 cases/100,000 pt-days to 11.7 cases/100,000 pt-days

- 79% reduction
- \( P<0.001 \)

BUT.......
Figured out along the way...

- Adequate isolation of known carriers critical, but not sufficient for effective containment of spread

- Also required: adequate identification of unknown carriers, meaning -
  - Active surveillance
  - Intervention in long-term care, the BLACK HOLE of CRE carriage

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012*
Guidelines for Active Surveillance

• Issued June 2008
  – Required in 3 groups
    • Contacts of CRE carriers newly identified on wards
      – Based on local infection control (IC) team investigation
      – In ICU or “step-down” unit – entire unit
    • High-risk groups on admission
      – Practically speaking in 2012 – anyone with admission to hospital or LTCF in past year
    • High-risk wards in hospital – at hospital’s discretion

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
First isolation of CRE


- Active surveillance: 59%
- Clinical culture: 41%


- Active surveillance: 80%
- Clinical culture: 20%

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
Requirement to check for carbapenemase

- As of 2009 –
  - All isolates must undergo MHT or KPC PCR
  - If PCR negative, must undergo MHT

- 95% of CRE isolates – carbapenemase producers

- Isolation policy:
  - carbapenemase-producing CRE – cohort, dedicated staff
  - Non-carbapenemase-producing CRE – “standard” contact isolation precautions

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012*
Cessation of CRE carrier status

• 2 negative rectal swab cultures
• Negative rectal swab carbapenemase gene PCR
• Negative culture from original site of isolation
  – If a clinical site
  – If still relevant

• Performed at discretion of IC staff in acute care; required in long-term care, after 90 days

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
Cessation of CRE carrier status

• Number of carriers who have become non-carriers (September 2009 - June 2012): ~1300

• Recrudescence: ~ 7%
  – Reasons
    • Re-infection
    • Changed conditions – antibiotics, illness, etc. – allow organism to re-emerge above threshold of detection

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
Intervention in long-term care

• Israel demographics
  – Population: ~ 8 million
  – Density: ~ 960/mi² (CA: ~240/mi²)
  – Acute-care beds: ~ 15,000 (=1.9 beds/1000 pop.)
  – Long-term-care beds: ~30,000
    • 3000 – post-acute care
    • 27,000 – chronic long-term nursing care
  – ~ 20% of CRE carriers discharged from acute care
    - to PAC (~500/year)

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012*
Intervention in long-term care

• Focused on post-acute care (PAC) facilities

• Elements of intervention
  – National staff established to conduct it – begun 2008
    • Physician
    • Nurse
    • Microbiologist
  – Data collection via email/fax
  – Regular site visits with written summaries
  – Evaluation based on 16-point Infection Control Score, including ward type-specific CRE isolation guidelines

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
Comparison Between 3 Surveys
Prevalence of CRE

Approximately 1000 patients with no history of CRE were screened in each survey

- 2011: 7.9%
- 2010: 9.1%
- 2008: 12.2%

P<0.001

Ben-David et al, ICAAC 2012
Intervention in community

- 2009: National mandatory guidelines issued for CRE isolation in ambulatory clinics
- Educational activities carried out by staff of National Center

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
CRE incidence by region, 2009-11
Nosocomial incidence per clinical cultures and surveillance; bacteremia

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
Class action lawsuit over super bug being prepared

Relatives of deadly bug's victims to sue bodies that allegedly failed to prevent its outbreak; 'there was no mention of hygienic regulations, standards no place in hospitals all over the world,' says.

48 carriers of super bug still in hospitals

Dozens still hospitalized with antibiotic-resistant bacterial infection, which had killed at least 120 as of Tuesday; health ministry to go on high alert

5 Talkbacks for this article

1. With 45 K lawyers in israel...they are all so busy
   A (03.09.07)
2. The only way they can sue the doctor
   David, Jerusalem (03.09.07)
3. Super bug kills dozens in hospitals across country

Super bug kills dozens in hospitals across country

Virulent strain of bacteria believed to be cause of death of 120-200 patients in hospitals. Experts explain most of those infected were already suffering from prior medical conditions. Health ministry says outbreak was kept secret to avoid mass panic

4. The only way they can sue the doctor
   David, Jerusalem (03.09.07)
5. Super bug kills dozens in hospitals across country

Super bug kills dozens in hospitals across country

Virulent strain of bacteria believed to be cause of death of 120-200 patients in hospitals. Experts explain most of those infected were already suffering from prior medical conditions. Health ministry says outbreak was kept secret to avoid mass panic

5 Talkbacks for this article

1. With 45 K lawyers in israel...they are all so busy
   A (03.09.07)
2. The only way they can sue the doctor
   David, Jerusalem (03.09.07)
3. Super bug kills dozens in hospitals across country

Super bug kills dozens in hospitals across country

Virulent strain of bacteria believed to be cause of death of 120-200 patients in hospitals. Experts explain most of those infected were already suffering from prior medical conditions. Health ministry says outbreak was kept secret to avoid mass panic
Targeted interventions using focused intra-regional comparisons

• Multi-year intervention in problematic LTCF
  – Site visits, screening, strict isolation measures, periodic closures
  – Point prevalence among unknown carriers decreased from
    \(~70\%\) to 7%  

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
Updated epidemic curve

CRE nosocomial acquisitions, clinical culture, general hospitals, Jan 2005 - July 2012

March 12, 2007: National guidelines issued
May 1, 2007: Task Force begins intervention
June 5, 2008: Screening guidelines issued

Retrospective data
Prospective data

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
Real-time communication network

- CRE status: permanent part of medical record

- At all times, the staff of the National Center is aware of the location of every CRE carrier hospitalized in the acute care and post-acute-care settings (and others)

- All movement of these carriers between facilities and into the outpatient setting is tracked

- The receiving institution (acute, LTCF, HMO) is notified in real time to ensure proper isolation in each setting

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012*
CRE acquisitions in hospitals

- Some MDRO acquisitions, particularly CRE, should be perceived as a violation of patient safety.

- As with HAIs, the responsibility for prevention is that of every employee in the institution – up to the CEO.

- CRE acquisition is preventable, should be perceived as a “system failure” → strictly follow specific facility-driven SOP for every episode.
  - **Goal**: getting to 0, staying at 0.

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012*

- Withholding reimbursements of CRE-related complications?
  - Would increase surveillances and resources allocation for preventive measures.
Summary

• CRE is endemic in Israeli healthcare facilities
  – No significant transmission detected in community
  – Large and persistent reservoir in LTCFs
  – Frequent and continuous movement of carriers between LTCFs and acute care

• Primary goal of national intervention:
  – to contain CRE spread in acute care setting

• Pillars of approach (carrier isolation/dedicated staffing/identification of silent carriers) remain effective

• Continued success requires recruitment and continued vigilance at every level of healthcare system

• No end in sight

*Courtesy of Israel National Center for Infection Control; Schwaber, ICAAC 2012
The “consumer side”

- Benchmark establishment
- Standardization:
  - Infection Control practices
  - Laboratory processing
- Monthly and Annual reports
- Direct notifications of carriers admitted
- Post-discharge follow-ups
- Molecular testing upon request on special circumstances (e.g. suspected SME in *Serratia*)
- Administrators are forced into the loop
what's the “real” modifiable risk factor?
• 3 “control” groups:
  – ESBLs
  – Susceptible Enterobacteriaceae
  – “un-infected”

• Matching criteria:
  – Time at risk
  – Hospital
  – Unit
  – Calendar year

• Matched analysis
# CRE Predictors Multivariate Analysis

## Table 2. Multivariable Models of Risk Factors for Enterobacteriaceae Isolation, Detroit Medical Center, September 1, 2008, to August 31, 2009

<table>
<thead>
<tr>
<th>Variablea</th>
<th>CRE vs uninfectedb</th>
<th>ESBL vs uninfectedb</th>
<th>Susceptible vs uninfectedb</th>
<th>CRE vs ESBL</th>
<th>CRE vs susceptible</th>
<th>CRE vs all controls combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
</tr>
<tr>
<td>Any antibiotic exposure in previous 3 months</td>
<td>11.4 (2.6–64.3) .006</td>
<td>1.7 (0.7–4.1) .24</td>
<td>5.2 (1.4–19.4) .015</td>
<td>12.3 (3.3–45) &lt;.001</td>
<td>7.1 (1.9–25.8) .003</td>
<td></td>
</tr>
<tr>
<td>Permanent residency in institution</td>
<td>1.04 (0.2–4.5) .96</td>
<td>1.3 (0.5–3.6) .56</td>
<td>0.15 (0.05–0.5) .002</td>
<td>2.1 (1–4.2) .05</td>
<td>5.3 (2.1–12.9) &lt;.001</td>
<td>2.6 (1.3–5.3) .01</td>
</tr>
<tr>
<td>Isolation of resistant bacteria in previous 6 monthsb</td>
<td>15.3 (4.2–55.6) &lt;.001</td>
<td>8.25 (2.7–25.7) &lt;.001</td>
<td>6.6 (1.9–23.3) .003</td>
<td>1.7 (0.76–3.7) .2</td>
<td>1.8 (0.7–4.7) .23</td>
<td>2.9 (1.4–5.7) .003</td>
</tr>
<tr>
<td>Dependent functional status in background</td>
<td>1.4 (0.5–4.4) .55</td>
<td>5.6 (2.1–14.7) .001</td>
<td>2.6 (1.1–6.4) .03</td>
<td>2.0 (0.76–3.7) .2</td>
<td>1.6 (0.6–4) .33</td>
<td>1.6 (0.6–4) .33</td>
</tr>
<tr>
<td>ICU stay in recent 3 months</td>
<td>1.3 (0.9–12.4) .02</td>
<td>5.2 (2.1–13.2) .001</td>
<td>3.0 (1.2–7.2) .02</td>
<td>1.6 (0.6–4) .34</td>
<td>1.36 (0.7–2.7) .37</td>
<td>2.7 (1.1–7.1) .04</td>
</tr>
<tr>
<td>Recent (6 months) invasive procedure</td>
<td>4.2 (1.2–15) .03</td>
<td>1.2 (0.4–3.4) .76</td>
<td>3.2 (1.3–8) .01</td>
<td>2.8 (1.1–7.6) .04</td>
<td>2.7 (1.1–7.1) .04</td>
<td>2.7 (1.1–7.1) .04</td>
</tr>
<tr>
<td>Charlson weighted index comorbidity ≥3</td>
<td>3.1 (0.8–11.8) .1</td>
<td>1.1 (0.4–2.7) .87</td>
<td>2.2 (0.9–5) .07</td>
<td>2.4 (1.03–5.6) .04</td>
<td>4.8 (1.9–12.5) .001</td>
<td>3.1 (1.4–7) .006</td>
</tr>
</tbody>
</table>

Note. CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase-producing Enterobacteriaceae; ICU, intensive care unit; OR, odds ratio.

a If a variable was not significant in bivariate analysis, it was not forced into the multivariable model.
b Part of the case-case-control analysis.
c Includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ESBL-producing *Enterobacteriaceae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.
## CRE Predictors Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRE vs. uninfected OR (CI-95%)</th>
<th>P</th>
<th>ESBL vs. uninfected OR (CI-95%)</th>
<th>P</th>
<th>Susceptible vs. uninfected OR (CI-95%)</th>
<th>P</th>
<th>CRE vs. ESBL OR (CI-95%)</th>
<th>P</th>
<th>CRE vs. susceptible OR (CI-95%)</th>
<th>P</th>
<th>CRE vs. all controls combined OR (CI-95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antibiotic exposure in previous 3 months</td>
<td>11.4 (2-64.3)</td>
<td>0.006</td>
<td>1.7 (0.7-4.1)</td>
<td>0.24</td>
<td>5.2 (1.4-19.4)</td>
<td>0.015</td>
<td>12.3 (3.3-45)</td>
<td>&lt;0.001</td>
<td>7.1 (1.9-25.8)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent residency in institution</td>
<td>1.04 (0.2-4.5)</td>
<td>0.96</td>
<td>1.3 (0.5-3.6)</td>
<td>0.56</td>
<td>0.15 (0.05-0.5)</td>
<td>0.002</td>
<td>2.1 (1-4.2)</td>
<td>0.05</td>
<td>5.3 (2.1-12.9)</td>
<td>&lt;0.001</td>
<td>2.6 (1.3-5.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Isolation of resistant bacteria in previous 6 months</td>
<td>15.3 (4.2-55.6)</td>
<td>&lt;0.001</td>
<td>8.25 (2.7-25.7)</td>
<td>&lt;0.001</td>
<td>6.6 (1.9-23.3)</td>
<td>0.003</td>
<td>1.7 (0.76-3.7)</td>
<td>0.2</td>
<td>1.8 (0.7-4.7)</td>
<td>0.23</td>
<td>2.9 (1.4-5.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Dependent functional status in background</td>
<td>1.4 (0.5-4.4)</td>
<td>0.55</td>
<td>5.6 (2.1-14.7)</td>
<td>0.001</td>
<td>2.6 (1.1-6.4)</td>
<td>0.03</td>
<td>2.0 (0.7-6.2)</td>
<td>0.2</td>
<td>1.6 (0.6-4)</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU stay in recent 3 months</td>
<td>3.9 (1.3-12.4)</td>
<td>0.02</td>
<td>5.2 (2.1-13.2)</td>
<td>0.001</td>
<td>3.0 (1.2-7.2)</td>
<td>0.02</td>
<td>1.6 (0.6-4)</td>
<td>0.34</td>
<td>1.36 (0.7-2.7)</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent (6 months) invasive procedure</td>
<td>4.2 (1.2-15)</td>
<td>0.03</td>
<td>1.2 (0.4-3.4)</td>
<td>0.76</td>
<td>3.2 (1.3-8)</td>
<td>0.01</td>
<td>2.8 (1.1-7.6)</td>
<td>0.04</td>
<td>1.6 (0.7-4)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson’s weighted Index Comorbidity ≥ 3</td>
<td>3.1 (0.8-11.8)</td>
<td>0.1</td>
<td>1.1 (0.4-2.7)</td>
<td>0.87</td>
<td>2.2 (0.94-5)</td>
<td>0.07</td>
<td>2.4 (1.03-5.6)</td>
<td>0.04</td>
<td>4.8 (1.9-12.5)</td>
<td>0.001</td>
<td>3.1 (1.4-7)</td>
<td>0.006</td>
</tr>
</tbody>
</table>
## Univariate Outcomes Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Died in hospital</th>
<th>Died within 3 months</th>
<th>Functional status deterioration</th>
<th>Discharged to LTCF</th>
<th>Additional hospitalizations within 6 months</th>
<th>Invasive procedure/surgery within 3 months</th>
<th>LOS after culture excluding dead</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRE vs. controls</strong></td>
<td>3.2 (1.4-7.2), 0.006</td>
<td>3.6 (1.6-7.9), 0.001</td>
<td>6.8 (3.1-15.3), p&lt;0.001</td>
<td>11.9 (5.0-28.1), p&lt;0.001</td>
<td>1.2 (0.6-2.2), 0.64</td>
<td>2.0 (1.1-3.9), 0.05</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>CRE vs. susceptible</strong></td>
<td>3.3 (1.5-7.5), 0.004</td>
<td>4.5 (1.9-10.3), p&lt;0.001</td>
<td>5.0 (2.3-10.8), p&lt;0.001</td>
<td>7.1 (3.1-16.3), p&lt;0.001</td>
<td>1.0 (0.5-1.8), 1.00</td>
<td>1.0 (0.6-1.9), 1.00</td>
<td>P=0.61</td>
</tr>
<tr>
<td><strong>CRE vs. ESBL</strong></td>
<td>1.8 (0.9-3.6), 0.15</td>
<td>1.7 (0.8-3.3), 0.17</td>
<td>5.1 (2.3-11.0), p&lt;0.001</td>
<td>5.6 (2.4-13.2), p&lt;0.001</td>
<td>1.2 (0.6-2.2), 0.75</td>
<td>1.1 (0.6-2.0), 0.87</td>
<td>P=0.42</td>
</tr>
<tr>
<td><strong>CRE vs. all 3 non-CRE groups combined</strong></td>
<td>2.6 (1.4-4.7), 0.003</td>
<td>2.8 (1.6-5.0), p=0.001</td>
<td>5.5 (2.9-10.6), p&lt;0.001</td>
<td>7.9 (3.9-16.0), p&lt;0.001</td>
<td>1.1 (0.7-1.8), 0.70</td>
<td>1.3 (0.8-2.2), 0.35</td>
<td>P=0.48</td>
</tr>
<tr>
<td><strong>ESBL vs. controls</strong></td>
<td>1.8 (0.8-4.2), 0.21</td>
<td>2.2 (1.0-4.9), 0.07</td>
<td>1.4 (0.6-2.9), 0.56</td>
<td>2.1 (0.9-4.9), 0.09</td>
<td>1.0 (0.5-1.9), 1.00</td>
<td>1.9 (1.0-3.5), 0.07</td>
<td>P=0.005</td>
</tr>
<tr>
<td><strong>Susceptibles vs. controls</strong></td>
<td>1.0 (0.4-2.4), 1.00</td>
<td>0.8 (0.3-2.1), 0.81</td>
<td>1.4 (0.6-2.9), 0.45</td>
<td>1.7 (0.7-3.8), 0.30</td>
<td>1.2 (0.7-2.2), 0.64</td>
<td>2.0 (1.0-3.7), 0.06</td>
<td>P=0.058</td>
</tr>
</tbody>
</table>
## In-Hospital Mortality Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRE vs. all 3 non-CRE groups combined</th>
<th>CRE vs. controls</th>
<th>CRE vs. susceptible controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (CI-95%)</td>
<td>P</td>
<td>OR (CI-95%)</td>
</tr>
<tr>
<td>CRE infection</td>
<td>1.43 (0.72-2.86)</td>
<td>0.308</td>
<td>1.18 (0.41-3.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.2 (0.82-5.92)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>1.28 (0.63-2.60)</td>
<td>0.50</td>
<td>2.04 (0.64-6.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.16 (0.42-3.18)</td>
</tr>
<tr>
<td>ICU stay in past 3 months</td>
<td>1.76 (0.91-3.40)</td>
<td>0.094</td>
<td>2.04 (0.74-5.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.95 (0.70-5.49)</td>
</tr>
<tr>
<td>Charlson’s combined condition score</td>
<td>5.11 (1.39-18.87)</td>
<td>0.014</td>
<td>4.37 (0.45-42.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.72 (0.65-50.8)</td>
</tr>
<tr>
<td>Dependent functional status</td>
<td>2.55 (1.0-6.48)</td>
<td>0.05</td>
<td>3.76 (0.94-14.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.10 (0.52-8.51)</td>
</tr>
<tr>
<td>Rapidly fatal McCabe score</td>
<td>2.49 (1.10-5.62)</td>
<td>0.029</td>
<td>1.51 (0.45-5.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.57 (0.48-5.09)</td>
</tr>
<tr>
<td>Body site of isolation: Blood</td>
<td></td>
<td></td>
<td>3.35 (1.21-9.28)</td>
</tr>
<tr>
<td>Constant</td>
<td>0.013</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
</tbody>
</table>
Brief report
The carbapenem-resistant Enterobacteriaceae score: A bedside score to rule out infection with carbapenem-resistant Enterobacteriaceae among hospitalized patients

Emily T. Martin MPH, PhD, Ryan Tansek BS, Vicki Collins MD, Kayoko Hayakawa MD, PhD, Odaliz Abreu-Lanfranco MD, Teena Chopra MD, Paul R. Lephart PhD, Jason M. Pogue PharmD, Keith S. Kay MD, MPH, Dror Marchaim MD

*Department of Pharmacy Practice, Wayne State University, Detroit, MI
Division of Infectious Diseases, Detroit Medical Center, Wayne State University, Detroit, MI
Department of Clinical Microbiology, Detroit Medical Center, Wayne State University, Detroit, MI
Department of Pharmacy Services, Detroit Medical Center, Wayne State University, Detroit, MI
FIG. 1. Time line and transmission opportunities among patients during the outbreak. Each row represents a patient, and each column represents a week. The colors represent the different units/wards as presented in the legend at the bottom. A transmission opportunity was deemed to have occurred if two patients were in the same ward during the same time period. For example, patients 1 and 2 had a transmission opportunity during week 12 in the Medicine 2 ward. Superscript a: week1, 29 March to 4 April 2009; week 24, 5 to 11 September 2009. Superscript b: date of clinical culture.
Colistin resistant CRE

• In case-control analysis:
  – The strongest independent predictor was co-colonization with a carbapenem-resistant non-fermenter (*P. aeruginosa* or *A. baumannii*)

• Confounder?
• Mobile genetic element crossing the inter-species barrier? i.e. VRSA scenario?
And story keeps evolve....

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study


Summary
Background Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-β-lactamase 1 (NDM-1) are potentially a major global health problem. We investigated the prevalence of NDM-1, in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK.
have occurred since the original isolate was discovered in 2008.\(^5\) In addition, isolates of Enterobacteriaceae-containing NDM-1 have now been characterized in the United States, Israel, Turkey, found in increasing numbers in isolates of Enterobacteriaceae obtained from outpatients throughout the world and, at the very least, will compromise our ability to use beta-lactam antibiotics resistant *Staphylococcus aureus*. Clin Infect Dis 2010;50:821-5.


Copyright \(\text{\textcopyright\textregistered\texttrademark\textregistered}\) 2010 Massachusetts Medical Society.

Letter to the Editor

Emergence of New Delhi metallo-\(\beta\)-lactamase in Jerusalem, Israel

sir,

New Delhi metallo-\(\beta\)-lactamase-1 (NDM-1) was first reported in *Klebsiella pneumoniae* and *Escherichia coli* in a Swedish patient returning from India [1]. After this seminal case, sporadic cases

2. Patient 2

In May 2011, a 74-year-old male

Zedek Medical Center for rehabilitation included uncontrolled diabetes hypoglycemia.
Ertapenem Resistance among Extended-Spectrum-β-Lactamase-Producing *Klebsiella pneumoniae* Isolates

Azita Leavitt, Inna Chmelnitsky, Raul Colodner, Itzhak Ofek, Yehuda Carmeli, and Shiri Navon-Venezia

The Laboratory for Molecular Epidemiology and Antibiotic Research, Division of Epidemiology, Tel Aviv Sourasky Medical Center—Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; Clinical Microbiology Laboratory, Ha’Emek Medical Center, Afula, Israel; and Department of Clinical Microbiology and Immunology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Received 7 April 2008/Returned for modification 19 September 2008/Accepted 3 February 2009

Ertapenem resistance in *Klebsiella pneumoniae* is rare. We report on an ertapenem-nonsusceptible phenotype among 25 out of 663 (3.77%) extended-spectrum-β-lactamase (ESBL)-producing *K. pneumoniae* isolates in a multicenter Israeli study. These isolates originated from six different hospitals and were multiclonal, belonging to 12 different genetic clones. Repeat testing using Etest and agar dilution confirmed ertapenem nonsusceptibility in only 15/663 (2.3%) of the isolates. The molecular mechanisms of ertapenem resistance in seven single-clone resistant isolates was due to the presence of ESBL genes (CTX-M-2 in four isolates, CTX-M-10 and OXA-4 in one isolates). OMPK36. Seven of 10 is

Introduction of OXA-48-producing Enterobacteriaceae to Israeli hospitals by medical tourism.


National Center for Infection Control, Israel Ministry of Health, Tel-Aviv, Israel. amosa@taasm.health.gov.il

**Abstract**

OBJECTIVES: The carbapenemase OXA-48 has been reported from different Mediterranean countries. It is mostly encoded on a single plasmid in various Enterobacteriaceae species. We characterized the epidemiological and molecular features of OXA-48-producing Enterobacteriaceae (OPE) in Israel.

METHODS: Epidemiological investigation was conducted by the National Center for Infection Control. Genotyping was performed using multilocus sequence typing. The bla(OXA-48)-carrying plasmids were investigated using S1 endonuclease and restriction fragment length polymorphism (RFLP). Conjugation efficiency of the bla(OXA-48)-carrying plasmids was studied in a filter mating experiment.
• Non-ST-258 KPC-producing *K. pneumoniae*
  • (Warburg et al, JAC 2012; Benenson et al, JAC 2012)

• NDM-1-producing CRE
  – 27 cases to date
  – Though some clearly acquired in hospital, no documented carriage among contacts, despite extensive screening

• OXA-48-producing CRE
  – 72 cases to date
  – Originally introduced by medical tourism (Adler et al, JAC 2011)
  – 48 cases due to **single-NICU outbreak** (primarily *Klebsiella*)

*Courtesy of Israel National Center for Infection Control*
Thanks!!!

- Mitchell J. Schwaber
- Yehuda Carmeli
- Keith S. Kaye
Questions?