Global Epidemiology of Carbapenem-Resistant Enterobacteriaceae (CRE)

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Mechanisms of carbapenem resistance in Enterobacteriaceae

- A combination of:
  - a $\beta$-lactamase that hydrolyzes carbapenems inefficiently
  +
  - a major porin loss

- An efficient carbapenem-hydrolyzing enzyme (carbapenamase)
\( \beta \)-lactamase hydrolyzing carbapenems inefficiently + porin loss

- ESBL or Ambler class C (AmpC) \( \beta \)-lactamase
- Major non-specific porin loss
- The phenotype is often ertapenem resistance and increased MICs of IMI and MER
Epidemiology and clinical consequences

- Sporadic cases arising during carbapenem therapy
- May lead to serious adverse clinical consequences
- May lead to treatment failure, e.g., breakthrough bacteremia
- Strains with limited ability to spread due to metabolic impairment conferred by major porin loss

Courtesy of Yehuda Carmeli
Relative growth rate in experimental *E. coli* strains

fitness cost incurred for major porin loss
(smaller fitness cost incurred for ESBL plasmid carriage)

*Figure 4.* Fitness of constructed and *in vitro*-selected mutants. The growth rate is calculated relative to the wild-type growth rate. Filled symbols show growth rates of mutants with pUUH239.2, while open symbols show mutants without pUUH239.2.
Major porin loss OmpK36 and combined OmpK36/35 reduce virulence in *K. pneumoniae* murine peritonitis model

Tsai YK et al, AAC 2011
Spread of non-carbapenemase – producing CRE

- **Portugal**
  - 4-month period, 2010
  - single hospital
  - 7 clonal CRE strains - 
    - CTX-M-15 (ESBL)-producing *K. pneumoniae* ST15 with a new OmpK36 porin variant

- **Italy**
  - Clonal outbreak of *K. pneumoniae* ST37 with OmpK35 loss and a new OmpK36 porin variant
  - Carbapenem resistance via combination with various plasmids carrying various ESBLs

Novais A et al, EJCMID 2012
Garcia-Fernandez A et al, AAC 2010
Infection control measures recommended for non-carbapenemase-producing CRE

- Likelihood of an outbreak are small
  - Contact precautions
  - Generally no need for contact screening
- If more than one case
  - Re-confirm that it is not a carbapenemase-producing strain
  - Examine clonality; if clonal – enhance IC measures
Carbapenemase-producing Enterobacteriaceae

- First reported from *S. marcescens* in 1982 – SME-1
  (Queenan AM and Bush K, CMR 2007)

- In past 30 years
  - Large variety of carbapenemases identified
  - Belong to 3 β-lactamase classes – A, B, D
Carbapenemase Genes

- Ambler Class A (serine beta-lactamases): 9 families
  - **KPC**, SME, NMC-A, IMI, PER, GES, SFO, SFC, IBC

- Ambler Class B (metallo-beta-lactamases): 6 families
  - **VIM**, GIM, SIM, **NDM**, **IMP**, SPM

- Ambler Class D: 2 families
  - **OXA**, PSE

Classification

- Phylogeny of carbapenemases

![Phylogeny diagram showing classes A, B, and D with specific enzymes like KPC-2, KPC-3, CTX-M15, SHV-12, TEM-12, OXA-48, OXA-181, IMP-8, IMP-1, AMP-C, VIM-1, and NDM-1.](Image)

Courtesy of Amos Adler
Carbapenemases and the pathogens that produce them

<table>
<thead>
<tr>
<th>Organism</th>
<th>Carbapenemases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Class A</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>++</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>+/-</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>+/-</td>
</tr>
<tr>
<td>Providencia spp.</td>
<td>+/-</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>+/-</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>+/-</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>+/-</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>+/-</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>+/−</td>
</tr>
<tr>
<td>Salmonella enterica</td>
<td>+/−</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>+</td>
</tr>
<tr>
<td>Pseudomonas putida</td>
<td>+</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>+</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>+</td>
</tr>
</tbody>
</table>

+++ high prevalence (>10%) in certain regions; ++, moderate prevalence (1–10%); +, low prevalence but >1 case; +/-, isolated cases; MBL, metallo-β-lactamase.

a Endemic in certain regions: VIM-1/4 in Greece and NDM-1 in India.
Carbapenemases – historical perspective

- First successful carbapenemase producers in Enterobacteriaceae:
  - 1996, North Carolina - KPC-2 in *K. pneumoniae*
  - 2001, Greece - VIM-1 in *E. coli* and *K. pneumoniae*
  - 2001, Turkey - OXA-48 in *K. pneumoniae*
  - 2008, Sweden - NDM-1 in *K. pneumoniae*
# Phenotypic characteristics

<table>
<thead>
<tr>
<th>Gene</th>
<th>Class</th>
<th>Predominant species</th>
<th>Inhibited by</th>
<th>β-lactams to which susceptible</th>
<th>Carbapenem MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC-2/3</td>
<td>A</td>
<td><em>K. pneumoniae</em></td>
<td>Boronic acid (partially by clavulanic acid)</td>
<td>-</td>
<td>High MIC$_{50}$=16</td>
</tr>
<tr>
<td>OXA-48</td>
<td>D</td>
<td>Variable</td>
<td>-</td>
<td>3$^{rd}$ gen ceph Aztreonam</td>
<td>Low (Higher w/ESBL &amp; porin changes – Nordmann, EID 2011)</td>
</tr>
<tr>
<td>NDM-1*</td>
<td>B</td>
<td>Variable</td>
<td>EDTA/DPA</td>
<td>Aztreonam</td>
<td>High MIC$_{50}$=16</td>
</tr>
<tr>
<td>VIM-1</td>
<td>B</td>
<td><em>K. pneumoniae</em></td>
<td>EDTA/DPA</td>
<td>Aztreonam</td>
<td>Low MIC$_{50}$=1</td>
</tr>
</tbody>
</table>

*NDM-1: MHT weak or even negative!

Courtesy of Amos Adler
Dissemination of carbapenemases

- Monoclonal
- Plasmid-borne
- Sub-plasmid elements
The Israeli Carbapenemase Story

KPC

- KPC: ~17,000
- OXA-48: ~80
- NDM-1: ~30
Great Britain:
Carbapenamase-producing isolates identified at the HPA

http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1294740725984
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*
KPC

- Found on plasmids
- 12 different KPC genes, most important KPC2, KPC3
- In many cases associated with single genetic element: transposon Tn4401 (Nordmann P et al, EID 2011)
- Outbreaks caused by K. pneumoniae, primarily single MLST type – ST 258
- US
  - First isolate from N. Carolina - 1996
  - Dissemination began early 2000s in northeast; since spread elsewhere
  - By 2007-10% of all isolates of K. pneumoniae reported to NHSN – carbapenem resistant (Hidron AI et al, ICHE 2008)
- Large outbreaks in Israel, Colombia, Greece, parts of China
- Sporadic reports throughout Europe, C. and S. America
- Smaller outbreaks involving KPC-producing E. coli, Enterobacter; have also been reported in nonfermenters
KPC – affected groups

- Risk factors for infection
  - Antibiotic use
  - ICU stay
  - Reduced functional status (Schwaber MJ et al, AAC 2008)

- Associated with acute-care and long-term care hospitals
  (Munoz-Price LS et al, ICHE 2010; Ben-David D et al, ICHE 2011)

- No significant community reservoir
KPC-producing CRE treatment options – *a bleak picture*

- Hydrolyze all $\beta$-lactams
  - Penicillins
  - Cephalosporins
  - Monobactams
  - Carbapenems

- Multiple associated co-resistances

- Susceptible only to polymyxins (colistin), +/- aminoglycosides (some), +/- tigecycline

  (Nordmann P et al, Lancet ID, 2009)
KPC-producing *K. pneumoniae*: a *triple* threat

- Highly effective at dissemination
- Highly resistant
- High mortality
  - Attributable overall 38%; attributable bacteremia 50%

(Patel G et al ICHE 2008; Schwaber MJ et al AAC 2008; Borer A et al ICHE 2009)
Dendrogram of the CDC's KPC-producing *K. pneumoniae* PFGE database (n = 248)

Predominance of a single clone – ST 258

Kitchel B et al, AAC, 2009
Global spread of KPC

Nordmann P et al, EID 2011
US Spread of ST 258

Kitchel B et al, AAC, 2009

CDC, September 2012
The Israeli picture

KPC first detected in \textit{E. coli}, \textit{Enterobacter} – KPC-2

Beginning in 2006 – spread of ST 258 clone of \textit{K. pneumoniae} – KPC-3

Since then ~17,000 patients infected with CRE; ~90\% \textit{K. pneumoniae} ST 258
Arrival in Hong Kong

- Urine sample from 75 y/o woman, frequent visitor to US, prior surgery in NY
- Active surveillance for CRE in Hong Kong introduced after this case
  - Pts with history of hospitalization, surgery or dialysis overseas in past 12 months
A carbapenem-resistant *Klebsiella pneumoniae* epidemic clone in Jerusalem: sequence type 512 carrying a plasmid encoding *aac(6')-Ib*

Gabriela Warburg¹, Carlos Hidalgo-Grass¹, Sally R. Partridge², Marcelo E. Tolmasky³, Violeta Temper¹, Allon E. Moses¹, Colin Block¹ and Jacob Strahilevitz²*

¹Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University, Jerusalem, 91120, Israel; ²Centre for Infectious Diseases and Microbiology, University of Sydney, Westmead Hospital, Sydney, New South Wales 2145, Australia; ³Center for Applied Biotechnology Studies, Department of Biological Science, College of Natural Sciences and Mathematics, California State University Fullerton, Fullerton, CA 92834-6885, USA

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ST11, the dominant clone of KPC-producing *Klebsiella pneumoniae* in China

Yan Qi¹,², Zeqing Wei³, Shujuan Ji¹, Xiaoxing Du¹, Ping Shen³ and Yunsong Yu¹*
The natural history of KPC (developed countries)

- In healthcare setting: acquisition and GI carriage
- 10-20% in acute care hospital will develop infection (>50% in transplant setting)
- Carriage may extended from few days to years, with ~50% clearance at 3 months
- In-hospital transmission extremely high; average of ~2 new acquisitions per non-isolated patient per hospital stay
- Explosive outbreaks may occur (“super-spreaders?”)
- Community spread and intra-familial transmission are extremely rare

Courtesy of Yehuda Carmeli
Regional spread among different types of healthcare facilities

Emergence and Rapid Regional Spread of *Klebsiella pneumoniae* Carbapenemase–Producing *Enterobacteriaceae*

Sarah Y. Won,¹,² L. Silvia Munoz-Price,³ Karen Lolans,⁴ Bala Hota,⁴,⁵ Robert A. Weinstein,⁴,⁵ and Mary K. Hayden⁴ for the Centers for Disease Control and Prevention Epicenter Program
- OXA-48 in Enterobacteriaceae - began in Turkey, spread throughout Mediterranean region – Lebanon, N. Africa, Europe, elsewhere

- OXA carbapenemases often seen in *Acinetobacter* – clonal spread

- In Enterobacteriaceae, spread largely via single plasmid; conjugation efficiency ~10,000-fold that of plasmid carrying KPC-3

- Walsh TR IJAA 2010

- Association with medical tourism - Adler A et al, JAC 2011
OXA-48, global picture

The Netherlands Germany Italy
Belgium
United Kingdom
France
Spain
Morocco
Algeria
Tunisia
Senegal

- Single OXA-48–producing isolates
- Outbreaks of OXA-48–producing isolates
- Nationwide distribution of OXA-48–producing isolates

Nordmann P et al, EID 2011
OXA-48

- Person-to-person spread documented
  - Rotterdam
    - *K. pneumoniae* ST395 (Poltron et al, CMI 2011)
  - Israel
    - 2012 NICU outbreak – Primarily *K. pneumoniae*

- Attributable mortality – not yet adequately documented
MBLs
VIM, IMP
NDM-1
VIM, IMP

- First acquired MBL:

- VIM & IMP
  - Endemic in Greece, Taiwan, Japan
  - Sporadic in many other countries
  - Death rates 18%-67%

- Nordmann P et al, EID 2011
Global spread of VIM and IMP

Nordmann P et al, EID 2011
Concomitant endemicity of 2 classes of carbapenemases: The Greek experience

Greece, Rate of Imipenem non-susceptible K. pneumoniae (clinical isolates)

% of imipenem non-susceptible K. pneumoniae

- Medical wards
- Surgical wards
- ICU

Period


KPC-2
VIM-1

Courtesy of Amos Adler
MBLs

**NDM-1 new kid on the block**

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

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

Yonsei University College of Medicine, Research Institute of Antimicrobial Resistance, Seoul, Republic of Korea; Department of Medical Microbiology, Cardiff University, Cardiff, United Kingdom; Clinical Microbiology, MTC—Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; Yonsei University College of Life Science and Biotechnology, Seoul, Republic of Korea; and Department of Clinical Microbiology, Orebro University Hospital, Orebro, Sweden

Received 10 June 2009/Returned for modification 7 August 2009/Accepted 10 September 2009
NDM

• Widespread in India and Pakistan 2005-2010
  – Detected when outbreaks in Europe traced to visitors to India and Pakistan

• Spread very likely by food and water

• Widely disseminated in New Delhi; contaminates tap and sewer water – Walsh TR et al, Lancet ID 2011
  • 30-70% of water sources sampled around New Delhi found contaminated with NDM
  • Estimated >100 million Indians carry NDM

• Medical tourism implicated here too – Kumarasamy KK et al, Lancet ID 2010
  • Extremely high risk of colonization in patients transferred from Indian hospital

• No significant spread in hospitals in developed countries

Courtesy of Yehuda Carmeli
NDM - features of spread

- NDM-1 gene not associated with clonal spread
  - Non-clonally related isolates and species
  - Mostly, but not exclusively, *E. coli* & *K. pneumoniae*
  - Hallmark is environmental spread

- Concern – identified in *E. coli* ST-131
  - Community strain
  - Same ST type mobilizes CTXM-15 ESBL
  - *E. coli* widespread pathogen worldwide; most common cause of pediatric diarrhea in India

Nordmann P et al, EID 2011
Complete Sequencing of pNDM-HK Encoding NDM-1 Carbapenemase from a Multidrug-Resistant *Escherichia coli* Strain Isolated in Hong Kong

Pak Leung Ho¹,²*, Wai U Lo¹, Man Kiu Yeung¹, Chi Ho Lin³, Kin Hung Chow¹, Irene Ang¹, Amy Hin Yan Tong³, Jessie Yun-Juan Bao³, Si Lok³, Janice Yee Chi Lo⁴
Global spread of NDM-1

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. (Nordmann P et al, EID 2011)
Concomitant global CRE epidemics?

1. Healthcare-associated
   - Carbapenemases of all types, esp KPC
   - Can be curtailed by appropriate surveillance and isolation measures in healthcare facilities

2. Community-acquired
   - Primarily NDM, OXA
   - Associated with poor public hygiene, world travel, overuse of antibiotics
   - Difficult to measure due to locations of prominence
   - Difficult to control
Time to sound the alarms??

Has the era of untreatable infections arrived?

David M. Livermore*

Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK
Can we contain KPC spread?

Yes!! - It is confined to the healthcare system

- Required:
  - Early detection of new introduction of colonized patients
  - Rapid response
  - Strict isolation
  - Coordinated regional control involving recruitment of the entire healthcare system
What about other carbapenamases?

- In developed countries, community spread is so far limited
  - Importation by tourism is important
- Prevention of spread in healthcare facilities is feasible
  - Requires structured, multifaceted regional action
- In some parts of the world, carbapenamases are spreading extensively in the community
  - Improved water systems, sanitation and hygiene are likely the most important interventions
Guidelines for control of spread

Advice on Carbapenemase Producers: Recognition, infection control and treatment

Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE)

2012 CRE Toolkit

Controlling the spread of carbapenemase-producing Gram-negatives: therapeutic approach and infection control

Thank you!

非常感谢

תודה רבה!