Emerging multi-resistant pathogens
where do they come from?
How to treat the patient?
How to limit the spread?

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Emerging MDR Gram negative rods (GNR)

- ESBL producing Enterobacteriaceae
- Carbapenem resistant GNR
  - *P. aeruginosa*
  - *A. baumannii* (will not be discussed)
  - Enterobacteriaceae
ESBLs are MDR

Susceptibilities of 1,030 ESBL producing *E. coli* & *Klebsiella* spp.

Colodner R. DMID 2007
ESBL producers

- TEM and SHV – were seen primarily in *Klebsiella pneumoniae* and were primarily hospital/LTCF acquired
- CTX-M has become the most common and important ESBL
  - Acquired several times during evolution from *Kluivera* spp.
  - seen in all species but most importantly in *E. coli*
  - Acquired in healthcare setting
  - Significant spread in the community
    - Food chain
    - Success of genes (CTX-M 14 and 15) and clones (ST 131)
Meta-synthesis for risk factors for ESBLs in non-hospitalized patients

- 191 articles identified
- 8 met the inclusion criteria, 6 were able to participate
  - 3 tertiary level hospitals (two from Spain [Seville and Barcelona] and one from Israel)
  - 1 networks of medical facilities in studies from Canada (Calgary Health Region)
  - France (28 private laboratories)
  - Turkey (15 geographically dispersed medical centers)
340 ESBL isolates: 87% E. coli
269 ESBL identified 65% CTX-M
Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis

Mitchell J. Schwaber¹* and Yehuda Carmeli¹,²

Mortality pOR=1.85

Delay in effective therapy pOR=5.56

JAC 2007
Mortality among 97 patients with adequate empiric therapy

Tumbarello M. AAC 2007
Preventive measures

• Based on local epidemiology
  – Specific targeted infections control measures
    • Where in-hospital spread is important and community spread is limited
  – Formulary interventions
    • Primarily cephalosporins and quinolones restriction
Increased Carbapenem consumption

• Likely to occur where ESBL become common
• Leads to fear of emergence and spread of carbapenem resistance
• Carbapenems are very effective agents resistant to hydrolysis by most beta-lactamases
Determinants of carbapenem Resistance

- An efficient carbapenemase or
  Combination of non-efficient beta-lactamase +
  porin loss +/- efflux
- Carbapenem entry to the cell (porins)
  - *P. aeruginosa* OprD – a specific porin used for
    influx of basic amino acids
  - Enterobacteriaceae - major porins
  - *A. baumannii* – various porins
Carbapenamases producers vs. porin mutants

• Carbapenamases
  – Almost all are plasmid mediated
  – Can be transferred and reach successful clones
  – Do not cause impairment to the bacteria
  – Are associated with outbreaks and clonal/gene spread

• Porin mutants
  – Selected under abx pressure
  – Lead to metabolic impairment
  – When major porin is lost, not associated with outbreaks
Imipenem resistance in *P. aeruginosa* due to OprD loss:

Nikaido H. Semin Cell Develop Biol. 2001;12;215

**Northern blot**

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<thead>
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<th></th>
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**Western blot**

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</table>
Correlation between group 2 carbapenem and imipenem resistant *P. aeruginosa*
Prevention

• Primarily control group 2 carbapenem use
• In case of evident in-hospital transmission targeted infection control measures
Mechanisms of Carbapenem Resistance in Enterobacteriaceae

- Efficient carbapenemases
  - Metallo-beta-lactamases (Class B)
    - VIM, IMP, NDM
  - Serine carbapenemases (Class 2f)
    - KPC, SME, NMC
- Other beta-lactamases (inefficient carbapenemases) + porin loss
  - Certain ESBLs + major porin loss
  - AmpC + major porin loss

Not associated with outbreaks
The Israeli experience with KPCs

- Carbapenem resistance in Enterbacteriaceae almost non-existing before 2006
- We have seen sporadic cases of KPC producing *Enterobacter* (NICU outbreak – imported by a mother) and *E. coli* in 2004-2005
- During 2006 large nationwide outbreak of KPC producing *K. pneumoniae*
% non-susceptibly to carbapenems of 1,030 ESBL producing *E. coli* & *Klebsiella* spp. Collected during 2004 (10 hospitals)

All detected as ESBL + porin loss,
No Carbapenamse, polyclonal

Adapted from Colodner R. DMID 2007; Leavit A, AAC 2009
Imipenem Resistant Enterobacter

- Seen for the first time in TASMC in Jan 2004 isolated from the urine of a surgical patient
  - Patient discharge before result – went unnoticed
- No other cases until Jun 2004
- Jun 30, 2004 – Outbreak in the NICU, three cases of late neonatal sepsis
  - 3 other carriers
- Traced to a mother which was GI carrier of the strain
Enterobacter KPC

• 2004 no further cases during 6 months
• 2005-2007:
  - 30 new cases, only two small (3 patients) time and space clusters
  - In hospital mortality 33%
    - Typical phenotype – quinolone and amikacin S
  - 18 isolates typed
    - 3 PFGE genotypes all produce KPC-2
      - 11 clone A
      - 5 clone B
      - 2 clone C
  - Repeated investigation did not identify the source
  - No association with carbapenem Rx

Similar plasmid encoding also for qnr B2

Marchaim D AAC 2008
Chmelintzky I. AAC 2009
KPC-2 producing *E. coli*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Isolate</th>
<th>Isolation Date</th>
<th>Infection site</th>
<th>LOS prior to IPM-R-<em>E. coli</em></th>
<th>LOS</th>
<th>antibiotic treatment</th>
<th>Infection/Colonization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>157</td>
<td>2/2005</td>
<td>Urine</td>
<td>10 d</td>
<td>14 d</td>
<td>FQ</td>
<td>No treatment</td>
<td>Colonized</td>
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<tr>
<td>2</td>
<td>329</td>
<td>9/2005</td>
<td>Blood</td>
<td>1 d *</td>
<td>3 d</td>
<td>No treatment</td>
<td>Empiric iv CRO</td>
<td>Died</td>
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<tr>
<td>3</td>
<td>339</td>
<td>9/2005</td>
<td>Subphrenic abscess</td>
<td>30 d</td>
<td>4 m</td>
<td>Broad-spectrum cephalosporins, FQ, metronidazole, VAN, Followed with 14d IPM until 2 w before isolation, and then TZP, AMK</td>
<td>TZP, AMK</td>
<td>Infection</td>
</tr>
<tr>
<td>4</td>
<td>360</td>
<td>10/2005</td>
<td>Urine</td>
<td>2 d *</td>
<td>18 d</td>
<td>CXM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>VAN, AMK, metronidazole</td>
<td>Colonized</td>
</tr>
</tbody>
</table>

<sup>a</sup> CXM: Cefuroxime

Navon-Venezia S. AAC 2006
IC at Dec 2005 in Tel Aviv

- KPC-2 in *E. coli* and *Enterobacter* spp.
- Mostly sporadic events
- High risk isolates
  - Single patient rooms
  - Contact isolation
  - Isolate on readmission admissions
- Presented to hospital management twice as a major threat
  - Questions regarding detection ability of the clinical micro lab (Vitek II system)
Antimicrobial susceptibility testing of 15 KPC-positive *K. pneumoniae* isolates

<table>
<thead>
<tr>
<th>Method (software)</th>
<th>Card/panel</th>
<th>Imipenem results (n = 15)</th>
<th>Meropenem results (n = 15)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Resistant</td>
<td>Intermediate</td>
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<tr>
<td>Broth microdilution</td>
<td>In-house frozen panel</td>
<td>13</td>
<td>2</td>
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<tr>
<td>Disk diffusion</td>
<td>BDDS disks</td>
<td>3</td>
<td>11</td>
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<tr>
<td>MicroScan (LabPro1.51,</td>
<td>Neg combo 32</td>
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<tr>
<td>Alert 1.50)</td>
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<tr>
<td>Phoenix (4.05W/3.81A)</td>
<td>NMIC/ ID-104</td>
<td>5</td>
<td>8</td>
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<tr>
<td>Sensititre AutoReader</td>
<td>GN2F</td>
<td>0</td>
<td>2</td>
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<tr>
<td>(3.0.8 SP2)</td>
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<td></td>
<td></td>
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<tr>
<td>VITEK (R10.01)</td>
<td>Superflex GNS 122 and 127</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>VITEK 2* (R04.01)</td>
<td>GN07</td>
<td>4</td>
<td>6</td>
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</tbody>
</table>

5 (33%) of 15 KPC-pos *K. pneumoniae* isolates were reported as susceptible to imipenem by VITEK 2

Tenover et al, EID 2006
Molecular epidemiology and emergence of KPC in carbapenem-resistant *K. pneumoniae*

Leavitt A., AAC, 2007
### Kleinella pneumoniae

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC</th>
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<tbody>
<tr>
<td>Amikacin</td>
<td>&gt;=64</td>
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<tr>
<td>Ampicillin</td>
<td>&gt;=32</td>
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<tr>
<td>Amp/Sulbactan</td>
<td>&gt;=32</td>
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<tr>
<td>Aztreonam</td>
<td>&gt;=64</td>
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<tr>
<td>Cefazolin</td>
<td>&gt;=64</td>
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<tr>
<td>Cefepime</td>
<td>&gt;=64</td>
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<td>Ceftazidime</td>
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<td>Ceftriaxone</td>
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<tr>
<td>Cefuroxime Axetil</td>
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<tr>
<td>Cefuroxime Sodium</td>
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<tr>
<td>Ciprofloxacin</td>
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<tr>
<td>Gentamicin</td>
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<tr>
<td>Piperacillin</td>
<td>&gt;=128</td>
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<td>Piperacillin/Taz</td>
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<tr>
<td>Tobramycin</td>
<td>&gt;=16</td>
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<tr>
<td>Trimeth/Sulfa</td>
<td>&gt;=320</td>
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<td>Levofloxacin</td>
<td>&gt;=8</td>
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<tr>
<td>Nitrofurantoin</td>
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<tr>
<td>Imipenem</td>
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<tr>
<td>Meropenem</td>
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Outcomes

• Crude Mortality
  – Resistant *Klebsiella* – 21 died (44%)
  – Susceptible *Klebsiella* – 7 died (13%)
  – No *Klebsiella* – 1 died (2%)

• Adjusted impact of CRKP on mortality:
  – Compared with hospital controls – OR 5.0 (1.7-14.8), p=0.004
  – Compared with susceptible *Klebsiella* – OR 3.9 (1.1-13.6), p=0.03

• Mortality with bacteremia >70%

Schwaber et al, AAC, 2008
Finkelstein, ECCMID 2007
Mid February

• Ministry of health approached to intervene at a national level

• Guidelines were written by IC society and embraced by the ministry of health mandating
  – Isolation
  – Cohorting with dedicated staff and equipment
  – Reporting daily on cases and isolation
  – National task force to control KPCs
Mode of action of the Task force

- Coordinated regional measures
- Collaborative effort of the entire IC community
- Refer to hospital CEO’s as responsible for control of CRE
- All formal communications are with the CEO’s
- Daily feedbacks for non-adherence
- Visits at all sites (30 per year)
Nationwide emergence of carbapenem-resistant Kpn - Israel

Incidence: 60-100 cases per 1,000 hospital beds/year
Total number of cases: ~1000 (per 7 million population) mortality 44%
PFGE of isolates from 8 hospitals and 5 LTCFs:

Navon-Venezia et al, ICAAC, 2007
Dendrogram of the CDC's KPC-producing *K. pneumoniae* PFGE database (n = 248)

**Predominance of a single clone - ST258**

Kitchel et al, AAC, 2009
Compliant hospitals succeed in containing spread; non-compliant hospitals do not.

These 2 non-compliant hospitals responsible for 30% of acquisitions this month.

Complete containment.
Not all-or-nothing: greater compliance yields greater containment

- Incidence vs Prevalence, Compliance < 60%
- Incidence vs Prevalence, Compliance 60% - 90%
- Incidence vs Prevalence, Compliance > 90%

Schwaber et al. ICAAC 2008
Effect of nationwide infection control intervention

First-Time CRE Acquisitions in Israeli General Hospitals, Jan. 2005-Jan 2009

March 12, 2007:
National guidelines issued

May 1, 2007:
Task Force begins intervention

June 5, 2008:
Screening guidelines issued
Effect of nationwide infection control intervention

First-Time CRE Acquisitions in Israeli General Hospitals, Jan. 2005-Jan 2009

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

Schwaber M. ICCAC 2009
Summary

• ESBL
  – Come from the community + healthcare spread
  – **Serious** infections should be treated with carbapenems
  – Prevention: Formulary interventions +/- targeted IC (local epidemiology)

• Porin loss mutants (primarily *P. aeruginosa*)
  – Caused by selective pressure
  – Treatment ?
  – Prevention: primarily abx control

• Carbapenemases
  – Come from other countries (or affected institutions)
  – Treatment?
  – Prevention: early detection and strict infection control measures