Multi-drug resistant Gram-negative infections
Epidemiology and diagnosis

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Challenges by XDR Gram-negatives

- Can cause severe, difficult-to-treat infections (impact on morbidity and mortality)
- Dearth of active antibiotics

Tuscany, November 2010 ....

62 y/o patient, hip replacement
Admitted to rehabilitation unit: pneumonia
Empirc treatment: ceftriaxone + levofloxacin
Does not improve
Transferred to district hospital
Empirc treatment: Meropenem + Linezolid

Does not Improve ...
Results of sputum culture:

K. pneumoniae

XDR phenotype

Definitive therapy?
Colistin (iv + aerosol)
Rifampin
Tigecycline
Meropenem

Initial improvement ...

Relapse after three days
Breakthrough bacteremia and septic shock

blood culture: K. pneumoniae

Outcomes of BSI caused by carbapenem-R K. pneumoniae

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Pts</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borer, ICHE 2009</td>
<td>Israel</td>
<td>32</td>
<td>crude: 72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>attributable: 50%</td>
</tr>
<tr>
<td>Nguyen, DMID 2010</td>
<td>USA</td>
<td>48</td>
<td>30-day: 42%</td>
</tr>
<tr>
<td>Mouloudi, ICHE 2010</td>
<td>Greece</td>
<td>19</td>
<td>In-hospital: MBL, 56%; KPC, 79%</td>
</tr>
<tr>
<td>Ben-David, CMI 2011</td>
<td>Israel</td>
<td>42</td>
<td>In-hospital: 69% infect.-related: 48%</td>
</tr>
<tr>
<td>Zarkotou, CMI 2011</td>
<td>Greece</td>
<td>53</td>
<td>Overall: 53%</td>
</tr>
<tr>
<td>Qureshi, AAC 2012</td>
<td>USA</td>
<td>41</td>
<td>28-day crude: 39%</td>
</tr>
<tr>
<td>Tumbarello, CID 2012</td>
<td>Italy</td>
<td>125</td>
<td>Overall: 42%</td>
</tr>
</tbody>
</table>

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Challenges by XDR Gram-negatives

- Can cause severe, difficult-to-treat infections (impact on morbidity and mortality)
- Dearth of active antibiotics
- Can spread rapidly and pandemically in health-care settings
- Are difficult to control

Proportion %

Year

Carbapenem-resistant Klebsiella pneumoniae, Italy

Proportion %

Year

Carbapenem-resistant Klebsiella pneumoniae, Italy

Proportion %

Year

Carbapenem-resistant Klebsiella pneumoniae

Proportion %

Year

Carbapenem-resistant Klebsiella pneumoniae, Europe 2011

Proportion %

Year

Greece

Italy
... but carbapenem-R enterics reported in most EU countries

Carbapenem resistance mechanisms in Enterobacteriaceae

- Porin loss + ESBL/AmpC production
  Lower-level R
  Not transferable

- Carbapenemase production
  Higher-level R
  Transferable
  - KPC
  - MBLs (NDM, VIM, IMP)
  - OXA-48-like

Carbapenem-resistant *Klebsiella pneumoniae*, Italy

Cross-sectional survey, 2011
(N=1964 *K. pneumoniae* isolates from 25 centers)
- 95% carbapenemase producers
- 87% KPC, 7% VIM, 1% OXA-48

Carbapenem-R *K. pneumoniae*, Italy

Cross-sectional survey, 2011
(N=1964 *K. pneumoniae* isolates from 25 centers)

KPC = *Klebsiella pneumoniae* carbapenemase

First isolates, late 1990s

- Imipenem
- Meropenem
- Amoxicillin
- Amoxicillin/Clavulanate
- Pip/tazo
- Ceftazidime
- Cefepime
- Cepodoxime
- Cefotaxime
- Ceftriaxone
- Aztreonam
- Gentamicin
- Tobramycin
- TMP/SMX
- Chloramphenicol

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K. pneumoniae CC258: a paradigm of High-Risk Clones (HiRiCs)

MDR bacterial clones retaining virulence and notable propensity for cross-transmission and spreading (“hyperepidemic”)

KPC-producing K. pneumoniae rapidly spreading and travelling overseas

NY: 30% of klebsiellae are carbapenem-R (KPC) by 2008

Nationwide outbreak, Israel carbapenem-R klebsiellae: - 2006: proportion, 11% - 2007: proportion, 22%

KPC-producing K. pneumoniae pandemic diffusion

Mostly clonal (CC258)

KPC-producing K. pneumoniae - Italian experience

The first reported cases of KPC-Kp (ST258)

KPC-producing K. pneumoniae from UK Labs confirmed to have carbapenemases

Enterobacteriaceae from UK Labs confirmed to have carbapenemases

Emergence of colistin-R KPC-Kp

Multifocal emergence of COL-R KPC-Kp
Also independent of COL exposure
Stable R phenotype
Variable proportions (6 - 45%)

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MDRGN – Epidemiology & Diagnosis
Gian Maria Rossolini, University of Florence, Italy
Broadcast live from the HIS/FIS conjoint conference www.hisconference.org.uk

**COL-R K. pneumoniae producing KPC**

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<tr>
<th>Antibiotic</th>
<th>MIC mg/L (S/I/R)</th>
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<td>Pip/Tazo</td>
<td>&gt;128 R</td>
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<td>Ceftazidime</td>
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<tr>
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<td>Gentamicin</td>
<td>&gt;64 R</td>
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<tr>
<td>Tobramycin</td>
<td>&gt;16 R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;4 R</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&gt;8 R</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>1.5 I</td>
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<td>Colistin</td>
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Isolated from blood and rectal swab of a 24 y/o neutropenic patient (induction for SCT) died of sepsis

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Isolated from sputum and rectal swab of a 20 y/o CF patient candidate for lung transplantation

**KPC-Kp: challenges to infection control**

- Propensity to colonise
  - Gut
  - Pharynx & resp. tract
  - Urinary tract

Rectal swab

High-level intestinal carriage

MER

MER + APB

Giani et al – J Hospital Infect 2012

**Persistent intestinal carriage of KPC-Kp**

- High-level carriage
- Low-level carriage
- Carriage not detectable

Giani et al – J Hospital Infect 2012

**Challenging XDR Gram-negatives: a long list**

- Carbapenem-R Enterics (CRE)
  - *K. pneumoniae* KPC
  - Enterics MBL+ (NDM, VIM)
  - *K. pneumoniae* OXA-48

**Pseudomonas aeruginosa producing metallo-beta-lactamase (MBL)**

Colistin Only Susceptible phenotype

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MBL+ P. aeruginosa: widespread in Europe

FIM-1, a New Acquired Metallo-
Lactamase from a Pseudomonas aeruginosa Clinical Isolate from Italy

Enzymes:
- VIM
- IMP
- GIM
- SPM
- NDM
- FIM

Sporadic cases or outbreaks

Challenging MDR Gram-negatives: a long list

- Carbapenem-R Enterics (CRE)
  - K. pneumoniae KPC
  - Enterics MBL+ (NDM, VIM)
  - K. pneumoniae OXA-48
- MBL-producing P. aeruginosa
- Carbapenem-R Acinetobacter (CRAB)

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<td>R</td>
</tr>
<tr>
<td>Colistin</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Amp/Sulbactam</td>
<td>16</td>
<td></td>
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Carbapenem-R Acinetobacter (CRAB)

CRAB data: first Italian surveillance (2011)

AMCLI-CoSA – Italian national surveillance 2011

Conclusions

- XDR Gram-negatives: now a major challenge in healthcare settings
- CRE are the major emerging issue globally, but XDR Acinetobacter and P. aeruginosa should not be neglected
- Dearth of new treatment options
- Surveillance and aggressive infection control, combined with antibiotic stewardship, remain the only reliable options to combat XDR Gram-negatives

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