Antimicrobials: a true ONE HEALTH issue: Background from a Medical Perspective

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Resistance among the Gram-positives
Problems with Resistance

- **Penicillin**
- **Chloramphenicol**
- **Tetracycline**
- **Erythromycin**
- **Vancomycin**
- **Gentamicin**
- **B-lactamase +ve S. aureus**
- **MRSA**
- **VRE**
- **↑CoNS infections**
- **↑CoNS infections**
- **CA-MRSA**
- **CA-MRSA?**
- **VISA**
- **VRSA**
- **Daptomycin**
- **Tigecycline**
- **Linezolid**
- **Synercid**
- **CA-CA-MRSA**
- **CA-CA-MRSA**
- **CA-CA-MRSA**
- **CA-CA-MRSA**
- **CA-CA-MRSA**
Staphylococcus aureus: Proportion of Invasive Isolates Resistant to Methicillin (MRSA), 2009

The symbols \(\uparrow\) and \(\downarrow\) indicate a significant increasing or decreasing trend for the period 2006-2009, respectively. These trends were calculated on laboratories that consistently reported during 2006-2009.

MRSA in Belgian acute care hospitals:
proportion of *S. aureus* clinical isolates and incidence of nosocomial acquisition

1994 - 2009

- Antibiotic use management teams
- MRSA new guidelines
- 1st Camp 2005
- 2nd Camp 2007
- 3rd Camp 2009

Source: National surveillance, B. Jans

Mean of rates in cohort of hospitals with min. 5 participations since 1994

National surveillance MRSA, Bea Jans
Counts of MRSA Bacteraemia
Oct 2005 to June 2009

A. Pearson and colleagues (HPA, Sept 2009)
Estimated Average Procurement of Alcohol Hand Rub and Liquid Soap in ml/bed-day, 2004-2007 in 148 acute NHS Trusts

- 3-fold increase in combined use to 60 ml per pt-day
- Analysis shows highly significant association between each ml of AHR used and 1% drop fall in MRSA BSI

Stone S et al. ECCMID 2009 (abstract O140)
Resistance among the Gram-negatives
The Gram-Negatives ... are Back!

Problems with Resistance

- Ampicillin
- Gentamicin
- 1st Gen Ceph
- 2nd Gen Ceph
- 3rd Gen Ceph
- Carbapenems
- Tigecycline
- Plasmid AmpC
- Acinetobacter infections
- P. aeruginosa infections
- Carbapenemases
- TEM
- TEM mutations
- FQs
- FQ resistance
- CTX-M ESBLs

Timeline:
- 1940
- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
- 2020
Multiple Mechanisms of Resistance in Gram-Negative Bacteria

- Loss of porins: carbapenems (imipenem)
- β-lactamases in periplasmic space: β-lactams (including carbapenems for some β-lactamases)
- Overexpression of transmembrane efflux pump: β-lactams (meropenem), quinolones, aminoglycosides, tetracycline antibiotics (tigecycline), and chloramphenicol
- Bypass targets: trimethoprim (dihydrofolate reductase), sulfonamides (dihydropteroate synthase)
- Ribosomal mutation or modification: tetracyclines (TetM or TetO), aminoglycosides (rRNA methylation)
- Mutations in lipopolysaccharide structure: polymyxin antibiotic class
- Antibiotic-modifying enzymes: aminoglycosides, ciprofloxacin
- Target mutations: quinolones (DNA gyrase and topoisomerase IV)

## Classification of β-Lactamases

<table>
<thead>
<tr>
<th>Class A</th>
<th>Class B</th>
<th>Class C</th>
<th>Class D</th>
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<tbody>
<tr>
<td>PC</td>
<td>IMP</td>
<td>AmpC</td>
<td>OXA-1, 10,</td>
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<tr>
<td>SHV-1, TEM-1, 2</td>
<td>VIM</td>
<td>CMY</td>
<td>OXA-11, 15</td>
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<td>SHV-&gt;1</td>
<td>KHM</td>
<td>ACT</td>
<td>OXA-23/27</td>
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<td>TEM-&gt;2</td>
<td>SPM</td>
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<td>24/40</td>
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<td>CTX-M</td>
<td>GIM</td>
<td>ACC</td>
<td>48, 51/66/69</td>
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<td>PER</td>
<td>SIM</td>
<td>FOX</td>
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<td>Metallo-β-Lactamases (MBLs)</td>
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Patel & Bonomo, Expert Rev Anti Infect Ther 2011; 9: 555 - 70
Resistance to Carbapenems among *K. pneumoniae*, EARS-net 2009

![Map showing resistance levels across Europe](image_url)
Resistance to Carbapenems among *K. pneumoniae* in Tzaneio General Hospital of Piraeus, Athens, Greece

**K. pneumoniae** BSI 2008-2010

- **CarbS**: 24; 22%
- **VIM**: 34; 31%
- **KPC**: 53; 47%
Treatments of last resort for infections with ESBL and carbapenemase-producing Gram-negatives
Tigecycline

• The first marketed member of glycylcyclines
• 9-t-butylglycylamido derivative of minocycline
• Evades common tetracycline efflux pumps and ribosomal protection mechanisms

BUT:

• Bacteriostatic mode of activity
• Many small observational studies
• Not good levels in blood
• Active against Enterobacteriaceae and Acinetobacter, but not against Pseudomonas
• Variable clinical effectiveness against Acinetobacter
• Emergence of resistance during treatment
Colistin

- Old (1950ies) bactericidal drugs, used as a prodrug (Colistin methanesulfonate, CMS)
- About 10 x more active against Gram-negative than Gram-positive bacteria

BUT:

- Inherent resistance: *Burkholderia cepacia*, *Serratia*, *Proteus*, *Bacteroides fragilis* … and most Gram-negative cocci
- CMS is a very inefficient prodrug (5 – 15% converted to colistin)
- Insufficient plasma concentrations, even at steady state
- Renal toxicity in up to 20% of patients
- Emergence of resistance during treatment
Resistance among KPC-Producing *K. pneumoniae* in Tzaneio General Hospital of Piraeus, Athens, Greece

Colistin resistance May 08- Oct 10: 27.8 % (41/180)
Non susceptibility to tigecycline: 2.8% (5/180)
Emergence of High Levels ESBL Producing Gram-negative Bacilli in the Asia-Pacific Region

New Delhi Metallo-1: The Mother of all β-Lactamases?

- \texttt{bla}_{\text{NDM-1}} (New Delhi Metallo-1):
  - Swedish patient of Indian origin who traveled to New Delhi
  - Acquired UTI in India
  - New Metallo-β-Lactamase (MBL) gene
  - Can hydrolyze all β-lactams except aztreonam
  - Located on a 180-kb (\textit{K. pneumoniae}) & 140-kb plasmid (\textit{E. coli}):
    - CMY-4 broadspectrum beta-lactamase
    - Genes inactivating ciprofloxacin, erythromycin, rifampicin, chloramphenicol, and aminoglycosides
    - Efflux pump genes
    - Growthpromoters genes that increase transcription
  - Potential for fast (global) spread

“The rapid dissemination of the \texttt{bla}_{\text{NDM-1}} carrying plasmids among clinical bacteria would be a nightmare scenario”

NDM-1 among Outpatients

- Objective: to study the prevalence of carbapenemase-producing Enterobacteriaceae in Pakistan
- Stool samples from 200 distinct patients in Rawalpindi, Pakistan
- 64 carbapenemase-positive isolates; only NDM-1 found
- Species:
  - *E. coli*: 30/64 isolates
  - *Enterobacter cloacae*: 21/64 isolates
- Prevalence:
  - Inpatients: 19/70 (27.1%)
  - Outpatients: 18/130 (13.8%)

Perry et al, J Antimicrob Chemother epub July 2011
Carbapenemase-Producing Enterobacteriaceae in the UK

Fig. 1. Carbapenemase-producing Enterobacteriaceae isolated in the UK (ARMRL referrals)
Why Are the Gram-negatives Worse? Because They Have More Sex...
Pandemic Spread of $bla_{CTX-M-15}$-ST131

- $bla_{CTX-M-15}$:
  - Located on multiple **plasmids** belonging to the incompatibility group IncFII
  - $bla_{CTX-M-15}$ mostly downstream IS$EcpI$
  - Multidrug co-resistance:
    - $bla_{OXA-1}$
    - $bla_{TEM-1}$
    - $aac6'-1b-cr$ (aminoglycoside acetyltransferase)
    - $tet(A)$ (tetracycline efflux protein), …

- **MLST clone ST131**
  - Disseminated by a widespread, successful **clone**: Serotype O25:H4-
    - MLST profile ST131
  - Causing urinary tract infections
  - O25:H4-ST131 not exclusively associated with $bla_{CTX-M-15}$
Plasmids Belonging to O25:H4-ST131

Complete Nucleotide Sequences of Plasmids pEK204, pEK499, and pEK516, Encoding CTX-M Enzymes in Three Major Escherichia coli Lineages from the United Kingdom, All Belonging to the International O25:H4-ST131 Clone.
Spread of MLST Clone ST131 in Canada

Distribution of the different ESBL-producing *Escherichia coli* isolates recovered from blood in the Calgary Health Region from 2000 to 2007.

Distribution of *Escherichia coli* MLST clone ST131 isolated from blood in the Calgary Health Region from 2000 to 2007.

Molecular Epidemiology of KPC-Producing *Klebsiella pneumoniae*
Isolates in the United States: Clonal Expansion of Multilocus Sequence Type 258<sup>7</sup>

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

Detection of the new metallo-β-lactamase VIM-19 along with KPC-2, CMY-2 and CTX-M-15 in *Klebsiella pneumoniae*

Spyros Pournaras<sup>1</sup>, Aggeliki Poulou<sup>2,3</sup>, Evangelia Voulgari<sup>3</sup>, Georgia Vrioni<sup>3</sup>, Ioulia Kristo<sup>1</sup> and Athanassios Tsakris<sup>3</sup>
Spread

- household members & pets
- animals
- travel
- food
High prevalence of multidrug-resistant (MDR) bacteria in developing countries → High risk for carriage and infection

- French study: 24/25 adoptees (Mali) positive for ESBL-producing Enterobacteriaceae (E-ESBL)
- Transmission of E-ESBL demonstrated for 5/22 (22%) families in which at least one family member other than the adoptee was found positive for E-ESBL

<table>
<thead>
<tr>
<th>β-Lactam resistance genes</th>
<th>E.coli, n (%)</th>
<th>Salmonella spp., n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX-M-15</td>
<td>6 (12.2)</td>
<td>-</td>
</tr>
<tr>
<td>CTX-M-15/TEM-1</td>
<td>36 (73.5)</td>
<td>-</td>
</tr>
<tr>
<td>SHV-12/TEM-1</td>
<td>4 (8.2)</td>
<td>4 (100.0)</td>
</tr>
<tr>
<td>SHV-2/TEM1</td>
<td>1 (2.0)</td>
<td>-</td>
</tr>
<tr>
<td>Unknown*</td>
<td>2 (4.1)</td>
<td>-</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>49 (100.0)</td>
<td>4 (100.0)</td>
</tr>
</tbody>
</table>

*: Isolates could not be recultured

International Travel (to India...) is a Risk Factor for Colonization with ESBL

<table>
<thead>
<tr>
<th>Continent or region</th>
<th>No. of travelers</th>
<th>No. (%) of travelers positive for ESBL-producing isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>25</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Asia (India excluded)</td>
<td>31</td>
<td>10 (32)</td>
</tr>
<tr>
<td>Central America</td>
<td>6</td>
<td>0 (0)</td>
</tr>
<tr>
<td>India</td>
<td>8</td>
<td>7 (88)</td>
</tr>
<tr>
<td>Middle East</td>
<td>14</td>
<td>4 (29)</td>
</tr>
<tr>
<td>North America</td>
<td>2</td>
<td>0 (0)</td>
</tr>
<tr>
<td>South America</td>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>16</td>
<td>2 (13)</td>
</tr>
</tbody>
</table>

*: The rate of acquisition of ESBL-producing strains was highest for travelers visiting India ($P < 0.001$)
Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains

**TABLE 1.** Distributions of extended-spectrum beta-lactamase (ESBL) genes in *Escherichia coli* and *Salmonella* spp. isolates from poultry, poultry retail meat samples and from human origin based on array results combined with sequence results

<table>
<thead>
<tr>
<th>Poultry-associated ESBL genes</th>
<th>Poultry</th>
<th>Poultry meat samples</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>n</em> = 35</td>
<td><em>n</em> = 81</td>
<td><em>n</em> = 409</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;CTX-M-1&lt;/sub&gt; (%)</td>
<td>49</td>
<td>49</td>
<td>24</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;TEM-32&lt;/sub&gt; (%)</td>
<td>29</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;SHV-12&lt;/sub&gt; (%)</td>
<td>0</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;TEM-2&lt;/sub&gt; (%)</td>
<td>11</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;CTX-M-2&lt;/sub&gt; (%)</td>
<td>9</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;TEM-30&lt;/sub&gt; (%)</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total (%)</td>
<td>100</td>
<td>100</td>
<td>35</td>
</tr>
</tbody>
</table>

The number of isolates analysed by array among meat and human isolates was 81 and 409, respectively. The number of isolates analysed by sequencing among poultry, meat and human isolates was 35 (100%), 81 (100%) and 208 (51%), respectively.

*Percentages are extrapolations based on array results and sequence results. For calculation of the percentages see also Fig. 1. For example percentage of *bla*<sub>CTX-M-1</sub> in human isolates = 0.84 × 0.85 × 0.34 = 24%.*

Leverstein *et al*, Clin Microbiol Infect 2011; 17: 873-80
Conclusions

• Resistance due to ESBLs and carbapenemases among Gram-negative bacilli is increasing worldwide
• This emergence is due to the global spread of highly transferable genes and successful clones,
• These genes are on mobile elements with resistance determinants to other classes of antibiotics
• ESBL and carbapenemases genes and strains are found in:
  – Animals
  – Food
  – Healthcare settings and outpatients
• Hence, control of this pandemic spread is challenging and therapeutic options are very limited
Does resistance matter?
Mortality in ESBL vs. non-ESBL Enterobacteriaceae Bacteraemia

What about new antibiotics?
New drugs Under Development

• New beta-lactamase inhibitors
• New beta-lactams
• New aminoglycosides
• Boron based small molecules
New Beta-Lactamase Inhibitor: NXL-104

- Cerexa/Novoxel/AstraZeneca
- Activity against carbapenem resistant Enterobacteriaceae
  - Most KPC producers (not if large amounts of AmpC as well)
  - *Acinetobacter* strains with OXA-48
  - Strains which are carbapenem resistant due to porin loss plus production of an ESBL or AmpC
- In phase 3 development
- BUT: No activity against MBL producers
Neoglycosides: ACHN-490

• Targeted against MDR *Enterobacteriaceae*
• In Phase 2 development
• BUT: Producers of 16S ribosomal RNA methylases are typically resistant to ACHN-490
• HENCE: Most MBL producers (including NDM producers) will be resistant to ACHN-490
“If you cannot measure it, you cannot improve it”

Lord Kelvin,
1824-1907
Total Outpatient Antibiotic Use in 33 European Countries in 2009

Adriaenssens et al., J Antimicrob Chemother 2011; Advance Access Published November 18, 2011
Belgian National Public Campaigns

- **When:** since November 2000, annually during winter season
- **Organised by:** BAPCOC (Belgian Antibiotic Policy Coordination Committee)
- **Budget:**
  - 400,000 EUR/annual campaign
- **Interventions targeting the public:**
  - Ads on TV, radio and newspaper
  - Information booklets
  - Folders
  - Posters
  - Internet campaigns: www.antibiotics-info.be
Outpatient Antibiotic Use in Belgium in Packages per 1,000 Inhabitants per Day – July – June. 1997 - 2008

Packages per 1000 inhabitants per day

-1.0%  -3.4%  -6.4%  -9.1%  -6.9%  -7.5%  -3.8%  -3.6%  -5.3%  -1.5%  -37%

-37%

Other J01 classes
Sulfonamides and trimethoprim (J01E)
Quinolones (J01M)
Macrolides, lincosamides and streptogramins (J01F)
Tetracyclines (J01A)
Cephalosporins and other beta-lactams (J01D)
Penicillins (J01C)
18 NOVEMBER
EAAD, 2008-2010

2008
Materials for general public
32 countries participated

2009
- Article in Eurosurveillance
- Materials for primary care prescribers
- Website translated in all EU languages, three TV spots developed
- 34 countries participated

2010
- 36 countries participated
- Materials for hospital prescribers
- Matched Get Smart week in the United States and the campaign in Canada

http://antibiotic.ecdc.europa.eu
• Antibiotic prescribing indicator: increased adherence to treatment guidelines for infections in outpatient care, and thereby a decrease in antibiotic prescribing.
  – Long term target for 2014: 250 prescriptions/1000 inhabitants and year
  – Target for 2011: decrease by 10% of the difference between current level and long term target

• The indicator was based on calculations from a diagnosis-prescribing study about respiratory tract infections in primary care

\[
\frac{95 \text{ prescriptions/1000 inhabitants}}{0.6 \text{ (primary care)} \times 0.7 \text{ (RTI)}} = 226 \text{ prescriptions/1000 inh.}
\]
Regional data Sweden

<table>
<thead>
<tr>
<th>NUTS</th>
<th>J01A</th>
<th>J01C</th>
<th>J01D</th>
<th>J01E</th>
<th>J01F</th>
<th>J01G</th>
<th>J01M</th>
<th>J01X</th>
<th>J01</th>
<th>Q4POP</th>
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<td>SE010</td>
<td>3.38</td>
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WHO Health Day, April 7, 2011

“We have watched too passively as the treasury of drugs that has served us well has been stripped of its value. We urge our colleagues worldwide to take responsibility for the protection of this precious resource. There is no longer time for silence and complacency”.