World wide resistance and multiresistance in *Escherichia coli*

*Escherichia coli*: an old friend with new tidings
Barcelona, Spain. 20 – 22 november, 2013

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SERVICIO DE MICROBIOLOGÍA Y PARASITOLOGÍA

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Escherichia coli, the main pathogen

- Responsible for nosocomial & community acquired infections
- Associated with sepsis, severe and mild infections
- Causing high number of deaths in the world
- Acquiring resistance mechanisms, including
  - multi-drug-resistance mechanisms
  - emerging resistance mechanisms

sensor of evolution of antimicrobial resistance
Escherichia coli: exchange from different compartments

Adapted from Woerther et al. Clin Microbiol Rev 2013; 26: 644-58
**World wide resistance in *Escherichia coli***

*Difficulties to obtain prospective sequential data*

- Absence of surveillance studies exclusively focused in *E. coli*
- Surveillance studies involving specific infections or anatomic locations, mostly focused in specific antibiotics
  - SENTRY (blood, urinary and intraabdominal isolates)
  - SMART (ertapenem and intraabdominal and urinary isolates)
  - TEST (tigecycline and selected Gram-negative pathogens)
  - MYSTIC (meropenem and selected Gram-negative pathogens)
- Data from surveillance studies partially and fractionally published according to:
  - specific geographic areas / countries
  - period of time
  - resistance problems
World wide resistance in *Escherichia coli*

The general perception (*difficult to disagree!*)

- Increasing prevalence of resistance to:
  - β-lactams: amoxicillin-clavulanate, extended spectrum cephalosporins (ESBLs), carbapenems (carbapenemases)
  - fluoroquinolones: isolates with topoisomerase mutations, plasmid mediated quinolone resistance mechanisms (PMQR)
  - aminoglycosides: isolates expressing modifying enzymes, methylases mediated resistance
  - other resistances: fosfomycin, trimetrophrim, trimetrophrim/sulfametoxyzol

- Emergence and dispersion of *multi-drug-resistance* isolates

- Dispersion of resistance isolates in different compartments
Multi-drug-resistance

- Cross resistance (class resistance)
  - a R mechanisms affecting antimicrobials from the same family
    - *E. coli* ciprofloxacin<sup>R</sup> (topoisomerase mutations)

- Multi-resistance (co-resistance)
  - different R mechanisms affecting different families of antimicrobials
    - ESBL producing *E. coli*
    - Carbapenemase producing *E. coli*

- Pleiotropic resistance
  - a single R mechanisms affecting antibiotics from different families
    - AcrAB-TolC hyper-expressing *E. coli*
Co-resistance and multi-resistance (*genetic capitalisms*)

- Resistant bacteria tend to be more resistant (multi-resistant)
  - easiest selection under antimicrobial pressure
    - accelerated process in scenarios with high selection density
    - co-selection by different antimicrobials
  - easy acquisition or resistance genes
    - opportunity of resistance strains ("clonal persistence")
    - genetic platforms adapted to acquire resistance genes

Baquero, Coque, Cantón. ASM News 2003; 69: 547-51
Canton, Ruiz-Garbajosa Curr Opin Pharmacol 2011; 11:477-85
**E. coli: selection of successful clones**

- \( \text{bla}_{\text{CTX-M-15}} \) in a multi-R island in specific plasmids (IncFII) and ecovars (B2) of specific *E. coli* (O:25:H4ST131)

Boyd et al. AAC 2004; 48:3758-64; Coque et al. EID 2008; 14:195-200
Nicolas-Chanoine et al. JAC 2008; 61:273-281
Emergence and dissemination of resistant bacteria

Fixation of resistant genes and resistant bacteria in bacterial populations

Mutation → Selection → Spread → Well-adapted clones

A = antibiotic pressure

Lateral transfer

Epidemic & endemic

A = by author

ESCMID Online Lecture Library

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Multi-drug-resistant organisms

(a) Sequential acquisition of resistance genes

(b) Co-selection process

susceptible isolate
resistance genes
isolate with co-resistance
antimicrobials

Canton & Ruiz-Garbajosa Curr Opin Pharmacol 2011; 11:477-85
- **4 plasmids with several resistance genes**

  - **p271A (35 kb, IncN):** \( b_{\text{NDM-1}} \)
  - **p271B (110 kb, IncF):** \( b_{\text{TEM-1}}, b_{\text{OXA-9}}, b_{\text{CTX-M-1}}, \) armA, aadA1, mph2, mel, dfrA12, arr2, cmlA5, sul1, qacE\( \Delta1 \)
  - **p271C (130 kb, Inc):** \( b_{\text{OXA-1}}, b_{\text{OXA-10}}, r_{\text{MTB}}, a_{\text{PhA1-LAB}}, \) ermB, catB4, sul1, qepA, qacE\( \Delta1 \)
  - **p271C (160 kb):** aadA6, aacC2, dfrA1, sul1, qacE\( \Delta1 \) merRTPADE

- **Chromosomal R-genes:** \( a_{\text{mpC}}, o_{\text{mpC}}, o_{\text{mpF}}, g_{\text{yrA}}, p_{\text{arC}} \)
Escherichia coli

- Which is the resistance pattern?
  - different location, gender, …

- Which are the important well establish resistance and emerging resistance mechanisms?
Escherichia coli: resistance pattern

143,583 routine clinical isolates
Comunitat Valenciana, Spain (2007-09)

Escherichia coli

Resistance according to anatomic location

X, men; O, women;
ABS, abscesses; DIS, digestive system; URI, urine; GUS, genitourinary system; MED, medical devices; BDT, bones and deep tissues; RES, respiratory system; BLO, blood; SST, skin and soft tissues.

Escherichia coli

Resistance according to gender and age

Graph showing the percentage of ciprofloxacin resistance by age and gender.
**Escherichia coli: resistance pattern**

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E. coli: amoxicillin-clavulanate resistance

- Hyperproduction of penicillinases (TEM-1, TEM-2, SHV-1)
  - Presence of strong promoters, small multi-copy plasmids
- OXA enzymes (poorly inhibited by β-lactamase inhibitors)
- IRT-(inhibitor-resistant TEM) and CMT-(complex-mutant TEM)
  - type β-lactamases
- Plasmid mediated AmpC enzymes
- Plasmid mediated carbapenemases
- Overproduction of constitutive AmpC cephalosporinase
- Permeability deficiency (OmpF and/or OmC)

Evolution of amoxicillin-clavulanic resistance blood isolates (Spain, EARSS-net, 2003-06) and antibiotic consumption

Amoxicillin-clavulanate resistant *E. coli*

257 isolates with amox/clav MIC ≥ 32/16 mg/l from clinical samples recovered in 7 hospitals in Spain (Jan-May 2010) with 9.3% of resistance

- **OXA-1-** and **IRT-producing isolates mainly recovered from UTIs**
- **OXA-1 producers and c-AmpC-high mainly recovered from blood**
- **No especific risk factors**


Rodríguez-Baño et al. J Clin Microbiol 2013; 51:2414-7

14.4% co-produced an ESBL most of them CTX-M-15
Escherichia coli: resistance pattern

143,583 routine clinical isolates
Comunitat Valenciana, Spain (2007-09)

ESBL producing *Escherichia coli* isolates

3rd gen. cephalosporin resistance (invasive isolates, 2003 vs. 2012)

ESBL producing *Escherichia coli* isolates

SMART study (intraabdominal infections)

Hawser et al., AAC, 2011;55:3917-3921; Hoban et al., AAC, 2010;54:3043-3046; Unpublished: SMART Study
ESBL producing *Escherichia coli* isolates

SMART study (intraabdominal infections)

Hawser et al., AAC, 2011;55:3917-3921;
Hoban et al., AAC, 2010;54:3043-3046; Unpublished: SMART Study
ESBL producing *Escherichia coli* isolates

SMART study (intraabdominal infections)

S. Hawser (unpublished, SMART Study)
CTX-M-Enterobacteriaceae: Global distribution

Hawkey and Jones. J Antimicrob Chemother 2009; 64 (Suppl. 1): i3-i10
Co-resistance in ESBL and non-ESBL producing *E. coli* isolates
ESBL – Enterobacteriaceae
Ramón y Cajal University Hospital (1988-2005)

320 patients in 2005!
65% outpatients mainly with UTI

Cantón & Coque. Curr Opin Microbiol 2006; 9:466-75
Fecal carriage of ESBL-Enterobacteriaceae

ESBLs, increasing the complexity

- Changing epidemiology of ESBLs (fecal carriers, Madrid, Spain)

Paniagua, Valverde et al. (submitted)
ESBL-Enterobacteriaceae fecal carriage

- WHO area
  - Africa
  - America
  - Eastern Mediterranean
  - Europe
  - South East Asia
  - Western Pacific

- Study size
  - 1,000
  - 500
  - 100

- Year: 2001 to 2011

*Escherichia coli*: resistance pattern

143,583 routine clinical isolates
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Current epidemiology of carbapenemases

- Increased prevalence all over the world:
  - efficient penetration with outburst of specific carbapenemases

- Mainly in Enterobacteriaceae (K. pneumoniae, Enterobacter spp., and E. coli) but also in P. aeruginosa and Acinetobacter baumanii

- Different epidemiology of different carbapenemases in distinct geographic areas
  - KPC mainly in EEUU
  - VIM, KPC and OXA-48 in Europe
  - NDM in India, Pakistan, ...

- Different population structure
  - dissemination of high-risk clones at initial
  - polyclonal situation

Nordmann et al. Emerging Infect Dis 2011; 17:1791- 8
Cantón et al. Clin Microbiol Infect 2012; 18:413-31
Carbapenemase producing Enterobacteriaceae

Carbapenem resistance (invasive isolates, 2012)

*Escherichia coli*  
*Klebsiella pneumoniae*

Emergence and dispersion of carbapenemases in *E. coli*

Monthly new patients infected/colonized with **KPC-producing-Enterobacteriaceae**. Ramón y Cajal University Hosp. (Sep-2009-Jan-2012)

Ruiz-Garbajosa et al. JAC; 2013, Jun-20
Fecal Carriage of Carbapenemase-Producing *Enterobacteriaceae*: a Hidden Reservoir in Hospitalized and Nonhospitalized Patients

Desirée Gijón, Tânia Curiao, Fernando Baquero, Teresa M. Coque, and Rafael Canton

<table>
<thead>
<tr>
<th>Species (no. of isolates)</th>
<th>PFGE type</th>
<th>Strain identification</th>
<th>MLST</th>
<th>Patient</th>
<th>Ward(s) and/or patient status</th>
<th>Month and year of isolation</th>
<th>Plasmid size(s) (kb)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Inc group</th>
<th>Integron type</th>
<th>Coresistance(s)</th>
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<td>Oncology&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>50, 100, 250</td>
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<td>Gm, Tb, Ak, Na, Fos, SXT</td>
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<td><em>Enterobacter cloacae</em> (3)</td>
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<td><em>Citrobacter freundii</em> (1)</td>
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<td>B</td>
<td>Na, SXT</td>
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</tbody>
</table>
Carbapenemase producing Enterobacteriaceae in Europe

OXA-48

- First identified in *K. pneumoniae* in Istanbul (Turkey) in 2003
- Extensively reported as a source of *K. pneumoniae* nosocomial outbreaks
- Well disseminated in the Mediterranean area and in western EU countries (cross-border dissemination)

Nordmann et al. Emerging Infect Dis 2011; 17:1791-8
Cantón et al. Clin Microbiol Infect 2012; 18:413-31

- Clonal and polyclonal spread
- Difficult detection unless in isolates:
  - coproducing an ESBL
  - with porin deficiency

Increasing description of OXA-48 in *E. coli*
### Population structure of OXA-48 - Enterobacteriaceae

#### Escherichia coli

<table>
<thead>
<tr>
<th>Country</th>
<th>ST</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>S38</td>
<td>Poirel et al. AAC 2011; 55:4937-8</td>
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<td>Italy</td>
<td>2076</td>
<td>Giani et al. AAC 2012; 56:2211-3</td>
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<td>UK</td>
<td>10, 38, 131, 88, 155, 167, 648,</td>
<td>Dimou et al. JAC 2012; April 24</td>
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<td>Ireland</td>
<td>131</td>
<td>Morris et al. AAC 2012; May 7</td>
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<td>Belgium</td>
<td>23, 648, 1722</td>
<td>Glupczynski et al. IJAA 2012; 39:168-72</td>
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<td>Israel</td>
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<td>Goren et al. JAC 2011; 66:672-3</td>
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<td>Sultanate of Oman</td>
<td>138, 648</td>
<td>Dortet et al. CMI 2012; 18:E144-8</td>
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</table>
**Escherichia coli: resistance pattern**

143,583 routine clinical isolates  
Comunitat Valenciana, Spain (2007-09)

Absence of cross resistance with other antimicrobials

Different resistance mechanisms
- Reduction of transport systems
  - Different mutations *in vivo* and *in vitro*
  - *ptsI* and *uhpA* mutants (regulation of GlpT and UhpT transporter)
- Target modification (MurA)
- Enzymatic inactivation
  - *fosA* (glutathione-S transferase) associated to plasmids
  - *fosB* (L-cysteine-thiol transferase) Gram-negatives
  - *fosX* (epoxide hydrolase): chromosomic (*L. monocytogenes*)
- FormA, FormB, FosC (quinases in fosfomycin producers)

Escherichia coli and fosfomycin

- Increased fosfomycin resistance in ESBL producers associated with increased use of this antimicrobial in the community

<table>
<thead>
<tr>
<th>Year</th>
<th>Fosfomycin resistance</th>
<th>ESBL production</th>
<th>Fosfomycin resistance in ESBL producers</th>
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<tr>
<td>2005</td>
<td>4.0%</td>
<td>6.0%</td>
<td>10.0%</td>
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<tr>
<td>2006</td>
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<td>10.5%</td>
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<td>2007</td>
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<td>7.0%</td>
<td>11.0%</td>
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<td>2008</td>
<td>5.5%</td>
<td>7.5%</td>
<td>11.5%</td>
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<tr>
<td>2009</td>
<td>6.0%</td>
<td>8.0%</td>
<td>12.0%</td>
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</tbody>
</table>

Fosfomycin-R: 9.1%  
- SHV-12: 5.1%  
- CTX-M-14: 5.6%  
- CTX-M-15: 15.3%
**Escherichia coli: world wide resistance**

- Increasing prevalence of resistant isolates
  - Well establish and emerging resistance mechanisms

- Different values according to surveillance studies

- Dispersion of multi-drug-resistant mechanisms ...
  - efficiently spread: clonal spread and polyclonal spread

- Sensor of resistance mechanism (central role in the acquisition and dissemination of resistance mechanisms)
World wide resistance and multiresistance in *Escherichia coli*