Epidemiology of Colistin Resistance

Po-Ren Hsueh
National Taiwan University Hospital
Deaths Attributable to Antimicrobial Resistance
Every Year by 2050 (>10 Million)
THE SPREAD OF ANTIBIOTIC RESISTANCE

An increasing proportion of bacteria display resistance to common antibiotics.

- Fluoroquinolones
- Cephalosporins (3rd gen)
- Aminoglycosides
- Carbapenems
- Polymyxins

*Enterobacteriae, including Escherichia coli, Klebsiella pneumonia, Enterobacter and Salmonella

© by author

Sara Reardon, 21 December 2015
Number of Citations in the PubMed Database
1960-Middle of 2011

Number of Citations in the PubMed Database
1955-2015 - Pigs

**Polymyxins**

**Facts**

- **Cationic polypeptides**
- **Colistin (polymyxin E)**
  - Originally from the soil bacterium *Paenibacillus polymyxa* subsp. *colistinus* in 1947
  - Colistimethate (inactive prodrug): transformed in body fluids
- **Polymyxin B**
  - Active antibiotic
  - Differ by only a single amino acid in the peptide ring, with a phenylalanine in polymyxin B and a leucine in colistin
- **Target**
  - Outer membrane of GNB, increasing the permeability of the bacterial membrane, leading to leakage of the cytoplasmic content and cell death

Structures of Colistin A and B, Colistimethate A and B, and Polymyxin B1 and B2

Dab, Diaminobutyric acid; Thr, Threonine; Phe, Phenylalanine; Leu, Leucine; L, Levogyre; D, Dextrogyre

- **X**: Fatty acid residue differing between the components of the mixtures: 6-methyloctanoic acid for colistin A and polymyxin B1, and 6-methylheptanoic acid for colistin B, and polymyxin B2
- **Y**: Aminoacid differing between colistin and polymyxin B: δ-Leu for colistin, and δ-Phe for polymyxin B
- **Z**: Groups differing between colistin/polymyxin B and colistimethate: -NH₂ for colistin and polymyxin B, and -NH-CH₂-SO₃H for colistimethate

# Colistin and Polymyxin B MIC Breakpoints

**CLSI and EUCAST, 2017**

<table>
<thead>
<tr>
<th>Criteria and bacterial groups</th>
<th>Colistin (µg/ml)</th>
<th>Polymyxin B (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td><strong>CLSI (M100-S27)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>≤2</td>
<td>-</td>
</tr>
<tr>
<td>A. baumannii complex</td>
<td>≤2</td>
<td>-</td>
</tr>
<tr>
<td><strong>EUCAST, 2017 (v.7.1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>≤2</td>
<td>-</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>≤2</td>
<td>-</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>≤2</td>
<td>-</td>
</tr>
<tr>
<td><strong>Colistin (CLSI)</strong></td>
<td>≤ 2 (WT)</td>
<td>≥ 4 (NWT)</td>
</tr>
</tbody>
</table>
# Prevalences of Colistin Resistance

## Overall Clinical Isolates of *K. pneumoniae*

### 2004-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Country (no. of isolates tested)</th>
<th>Multi-(M) or single center (S)</th>
<th>% of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004-2005</td>
<td>Singapore (16)</td>
<td>S</td>
<td>6</td>
</tr>
<tr>
<td>2006-2007</td>
<td>South Korea (221)</td>
<td>M</td>
<td>10.9</td>
</tr>
<tr>
<td>2007-2008</td>
<td>Canada (515)</td>
<td>M (national)</td>
<td>2.9</td>
</tr>
<tr>
<td>2006-2009</td>
<td>Worldwide (9,774)</td>
<td>M (SENTRY)</td>
<td>1.5</td>
</tr>
<tr>
<td>2013-2014</td>
<td>USA (1,2205)</td>
<td>M</td>
<td>4</td>
</tr>
<tr>
<td>2014-2015</td>
<td>Worldwide (7,480)</td>
<td>M (SENTRY)</td>
<td>4.4</td>
</tr>
</tbody>
</table>

## Prevalences of Colistin Resistance

Clinical Isolates of Carbapenem-R *K. pneumoniae*

### 2003-2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Country (no. of isolates tested)</th>
<th>Multi-(M) or single center (S)</th>
<th>% of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-2004</td>
<td>USA (96)</td>
<td>M</td>
<td>9</td>
</tr>
<tr>
<td>2006-2007</td>
<td>Israel (88)</td>
<td>S</td>
<td>4.5</td>
</tr>
<tr>
<td>2009-2010</td>
<td>China (68)</td>
<td>S</td>
<td>4.4</td>
</tr>
<tr>
<td>2010</td>
<td>Greece (120)</td>
<td>S</td>
<td>20.8</td>
</tr>
<tr>
<td>2010-2011</td>
<td>Italy (97)</td>
<td>M</td>
<td>36.1</td>
</tr>
<tr>
<td>2010-2012</td>
<td>Spain (79)</td>
<td>M</td>
<td>22.8</td>
</tr>
<tr>
<td>2012</td>
<td>Taiwan (247)</td>
<td>M (National)</td>
<td>12.1</td>
</tr>
<tr>
<td>2010-2013</td>
<td>Greece (92)</td>
<td>S</td>
<td>21.7</td>
</tr>
<tr>
<td>2014</td>
<td>Italy (214)</td>
<td>S (ICU)</td>
<td>21.9</td>
</tr>
<tr>
<td>2013-2014</td>
<td>Italy (178)</td>
<td>M (national)</td>
<td>43</td>
</tr>
<tr>
<td>2014</td>
<td>France (561)</td>
<td>M (National)</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Outbreaks Caused by Colistin-resistant, Carbapenemase-producing *K. pneumoniae*

Each star indicates a single report

# High Colistin Resistance in Enterobacteriaceae from Pigs According to Their Health Status

<table>
<thead>
<tr>
<th>Country</th>
<th>Bacteria</th>
<th>Health status of pigs</th>
<th>% resistance (in order)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td><em>E. coli</em></td>
<td>Symptoms of <em>E. coli</em> infection</td>
<td>35.6</td>
</tr>
<tr>
<td>UK</td>
<td><em>E. coli</em></td>
<td>Clinical healthy (slaughterhouse)</td>
<td>34.1</td>
</tr>
<tr>
<td>China</td>
<td><em>E. coli</em></td>
<td>N/A</td>
<td>33.3</td>
</tr>
<tr>
<td>Spain</td>
<td><em>E. coli</em></td>
<td>Diarrhoea, oedema disease</td>
<td>26.7</td>
</tr>
<tr>
<td>Brazil</td>
<td><em>Salmonella enterica</em></td>
<td>Enterocolitis</td>
<td>21</td>
</tr>
<tr>
<td>Lithuania</td>
<td><em>Salmonella Choleraesuis</em></td>
<td>Clinical symptoms</td>
<td>17</td>
</tr>
<tr>
<td>Belgium</td>
<td><em>E. coli</em></td>
<td>Diarrhoea</td>
<td>13.2</td>
</tr>
<tr>
<td>Belgium</td>
<td><em>E. coli</em></td>
<td>Symptoms of <em>E. coli</em> infection</td>
<td>9.6</td>
</tr>
<tr>
<td>Brazil</td>
<td><em>E. coli</em></td>
<td>PWD or oedema disease</td>
<td>6.3</td>
</tr>
<tr>
<td>Europe</td>
<td><em>Salmonella spp.</em></td>
<td>Clinical healthy (slaughterhouse)</td>
<td>6.3</td>
</tr>
<tr>
<td>Europe</td>
<td><em>E. coli</em></td>
<td>Clinical healthy (slaughterhouse)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

- A *E. coli* strain, SHP45, possessing colistin resistance from a pig
  - MCR-1 (mediated by *mcr-1*) is a member of the phosphoethanolamine transferase enzyme, with expression resulting in the addition of phosphoethanolamine to lipid A
  - Plasmid carrying *mcr-1* was mobilised to an *E. coli* recipient (frequency of $10^{-1}$ to $10^{-3}$ cells per recipient cell) by conjugation, and maintained in *K. pneumoniae* and *P. aeruginosa*
  - In an in-vivo model, MCR-1 negated the efficacy of colistin

- *mcr-1* carriage in *E. coli* isolates (2011-4)
  - 15% in raw meat (78/523), 21% in animals (166/804), and 1% (16/1,322) in humans

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

<table>
<thead>
<tr>
<th>Year</th>
<th>Positive isolates (%)/number of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Escherichia coli</strong></td>
</tr>
<tr>
<td></td>
<td>Pigs at slaughter 2012 31 (14.4%)/216</td>
</tr>
<tr>
<td></td>
<td>Pigs at slaughter 2013 68 (25.4%)/268</td>
</tr>
<tr>
<td></td>
<td>Pigs at slaughter 2014 67 (20.9%)/320</td>
</tr>
<tr>
<td></td>
<td>Retail meat All 78 (14.9%)/523</td>
</tr>
<tr>
<td></td>
<td>Chicken 2011 10 (4.9%)/206</td>
</tr>
<tr>
<td></td>
<td>Pork 2011 3 (6.3%)/48</td>
</tr>
<tr>
<td></td>
<td>Chicken 2013 4 (25.0%)/16</td>
</tr>
<tr>
<td></td>
<td>Pork 2013 11 (22.9%)/48</td>
</tr>
<tr>
<td></td>
<td>Chicken 2014 21 (28.0%)/75</td>
</tr>
<tr>
<td></td>
<td>Pork 2014 29 (22.3%)/130</td>
</tr>
<tr>
<td></td>
<td>Inpatient 2014 13 (1.4%)/902</td>
</tr>
<tr>
<td></td>
<td><strong>Klebsiella pneumoniae</strong></td>
</tr>
<tr>
<td></td>
<td>Inpatient 2014 3 (0.7%)/420</td>
</tr>
</tbody>
</table>

Table 2: Prevalence of colistin resistance gene mcr-1 by origin

Detection of mcr-1 among Enterobacteriaceae
SENTRY 2014-2015, Humans

- *E. coli* (n=13,526) and *K. pneumoniae* (n=7,480) in 183 hospitals located in the Asia-Pacific region (n=15), Europe (n=46), Latin America (n=9), and North America (n=113)

- Colistin MICs of $\geq 4$ mg/L in *E. coli*
  - 0.4% (n=59)
  - 32.2% (19/59) positive for *mcr-1* in 2014 (n=8), 2015 (n=11)
  - Asia: Hong Kong (n=1), Malaysia (n=1)

- Colistin MICs of $\geq 4$ mg/L in *K. pneumoniae*
  - 4.4% (n=331)
  - All negative for *mcr-1*

- Colistin MICs of $\geq 4$ mg/L in all isolates: 1.9% (390/21,006)

Recovery of \textit{mcr-1}–Expressing Resistant Enterobacteriaceae Isolates

As of June 21, 2016

Colistin resistance gene \textit{mcr-1} in \textit{Escherichia coli} isolates from humans and retail meats, Taiwan


Global Distribution of Plasmid-mediated mcr-1 Colistin-resistant Strains from Environments, Foods, Animals and Humans (November 2015 to April 2016)- 1010 Isolates

Total no. of bacteria bearing mcr-1, n = 1010

Global Distribution of Plasmid-mediated mcr-1 Colistin-resistant Strains from Environments, Foods, Animals and Humans (November 2015 to April 2016)

As of 1 Sept. 2016 (country)
Humans (n=29) Animals (n=22)

### Countries Where the mcr-1 Gene Isolated from Enterobacteriaceae in Pigs and other Farm Animals

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of report</th>
<th>Animal production</th>
<th>Bacterial species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laos</td>
<td>2015</td>
<td>Pigs</td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td>Denmark</td>
<td>2015</td>
<td>Chicken</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>China</td>
<td>2016</td>
<td>Pigs, chicken</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>Algeria</td>
<td>2016</td>
<td>Chicken</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>Vietnam</td>
<td>2016</td>
<td>Pigs</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>France</td>
<td>2016</td>
<td>Veal calves</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>Germany</td>
<td>2016</td>
<td>Pigs</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>Malaysia</td>
<td>2016</td>
<td>Pigs</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>Japan</td>
<td>2016</td>
<td>Cattle, pigs</td>
<td><em>E. coli, Salmonella</em></td>
</tr>
<tr>
<td>UK</td>
<td>2016</td>
<td>Pigs</td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>Belgium</td>
<td>2016</td>
<td>Pigs, calves</td>
<td><em>E. coli</em></td>
</tr>
</tbody>
</table>

**mcr-1-positive Enterobacteriaceae**

Human Colonization, China

- MCRPEC colonization: 0.65% (19/2,923) rectal swabs from healthy volunteers and 2.92% (35/1,200) rectal swabs from patients
  - Antibiotic use before hospital admission (p<0.0001) and living next to a farm (p=0.03) were associated with MCRPEC carriage in 35 patients compared with 378 patients with mcr-1-negative *E coli* colonization

- MLST and plasmid analysis shows that MCRPEC are diversely spread throughout China and pervasive in Chinese communities

Colistin Resistant Enterobacteriaceae from Fecal Flora - Absence of mcr-1, mcr-2
Healthy Humans (N=1,091) and Primary Care Patients (N=53)

- 18 were resistant to colistin (MIC >2 mg/L)
  - Healthy humans (n=16, 1.5%), patients (n=2, 3.8%)
  - Hafnia alvei (n=9), E. coli (n=3), E. cloacae (n=4), K. pneumoniae (n=1) and Raoultella ornithinolytica (n=1)
  - All negative for mcr-1 and mcr-2

- The risk of transfer of mcr genes from animals, food or the environment is currently very low in the community, despite the fact that colistin is used for treating infections in livestock
  - Switzerland: none mcr-1 and mcr-2 (food-producing animals)
  - Swiss: 25.8% (poultry meat, partly imported) in retail stores contain mcr-1 harboring E. coli

Two hospitals in Zhejiang and Guangdong

*mcr-1*-positive *Enterobacteriaceae*

Human Infection, China

- Two hospitals in Zhejiang and Guangdong
- *mcr-1* was detected in 76 (1%) of 5,332 *E coli* isolates, 13 (<1%) of 348 *K. pneumoniae*, one (<1%) of 890 *E. cloacae*, and one (1%) of 162 *E. aerogenes*
- MCRPEC infection was associated with male sex (*p*=0·011), immunosuppression (*p*=0·011), and antibiotic use, particularly carbapenems (*p*=0·002) and fluoroquinolones (*p*=0·017), before hospital admission

**mcr-1-positive Enterobacteriaceae**

**Human BSI, China**

- Bloodstream infections (BSI) at 28 hospitals in China

- *mcr-1* Positive (n=21)
  - 1% (20/1,495) *E. coli*, <1% (1/571) *K. pneumoniae*
  - Colistin MICs of 4-32 mg/L (but one 0.06 mg/L)
  - Clonally diverse and on two types of plasmids, a 33 kb IncX4 plasmid and a 61 kb Inc12 plasmid
  - All susceptible to tigecycline and 95% susceptible to the carbapenem and β-lactamase inhibitor combination piperacillin and tazobactam
  - 30 day mortality 0%

**mcr-1 in Enterobacteriaceae from Companion Animals**

Beijing, China, 2012–2016

- Possible transmission of *mcr-1*-harboring *E. coli* between companion animals and human
  - One man worker, 4 dogs and 2 cats in the pet store
- 1,439 nasal and rectal swab samples collected from 1,254 dogs and 185 cats
  - 566 *Enterobacteriaceae*: 14% (79/566) colistin-R
  - *mcr-1* gene: 8.7% (49/566) of all isolates and 62.0% (49/79) of colistin-R isolates (*47 E. coli* and 2 *K. pneumoniae*)
- 32 nasal swab samples from the pet owners
  - 25 *Enterobacteriaceae* strains isolated
  - Only 1 *E. coli* colistin-resistant and *mcr-1*-positive

mcr-1 in Enterobacteriaceae from Companion Animals
Beijing, China, 2012–2016

- mcr-1–positive *E. coli* from the pet owner and pets
  - Same PFGE pattern and ST 101 as 5 isolates from dogs and cats
  - *E. coli* strains can be exchanged between companion animals and humans

- 35 pet food samples
  - 7 positive for *mcr-1*
  - 5 food from China and one each from Italy and Belgium
  - Pet foods may be a source from which intestinal bacteria of companion animals can acquire the *mcr-1* gene

Emergence of the \textit{mcr-1} colistin resistance gene in carbapenem-resistant Enterobacteriaceae


Carbapenem-resistant and colistin-resistant \textit{E. coli} co-producing NDM-9 and MCR-1


Worrisome spread of the \textit{mcr-1} gene in \textit{E. coli} in the community across at least three continents (China, Loa, Europe)

Arcilla MS et al. \textit{Lancet Infect Dis} 2016;16:147-9..
**Transmission Routes of blaNDM and mcr-1**

**China**

- **Black circles**: different sections in the poultry-producing chain
- **Red and blue arrows**: possible transmission routes of blaNDM and mcr-1
- **Large circle**: transmission route of blaNDM and mcr-1 in different hosts from commercial chicken farm B
- **Red dashed lines**: transmission of blaNDM between humans and birds from the poultry-producing chain

---

It is likely that MCR-1-mediated colistin resistance originated in animals and subsequently spread to people.

'Limit or stop using polymixins in agriculture'
Trends in Consumption of Polymyxins in European Countries, ECDC, 2014

DDD, defined daily doses

Comprehensive Resistome Analysis Reveals the Prevalence of NDM and MCR-1 in Chinese Poultry Production - China

- By 2030, global poultry production, 8.5 billion
  - China is a key producer
- From April 2017, withdrawal of colistin (growth promoter)
  - Removing over 8,000 tones/year from the Chinese farming sector
- The impact of banning colistin and the epidemiology of MDR E. coli (using \( \text{bla}_{\text{NDM}} \) and \( mcr-1 \) as marker genes)
  - \( mcr-1 \), but not \( \text{bla}_{\text{NDM}} \), is prevalent in hatcheries, but \( \text{bla}_{\text{NDM}} \) quickly contaminates flocks through dogs, flies and wild birds
  - WGS: common \( \text{bla}_{\text{NDM}} \)-positive E. coli shared among farms, flies, dogs and farmers, providing direct evidence of carbapenem-resistant E. coli transmission and environmental contamination

Colistin Resistance in
P. aeruginosa and A. baumannii

- **P. aeruginosa**
  - SENTRY (2009-2011, n=2,383): <0.7%
  - 31 medical centres from 13 European countries (2011-2012, n=2191): 0.2% among MDR
  - Greece (2011-2012, n=881 HA): 6.3%
  - Canada (2008-2015, n=2,906): 5.1%
  - Korea (2015, n=215): 4.2%; 27.3% of IMP-6-ST235 isolates (9/33)
  - India (2012-2013, n=352): 3.8-2.2%

- **A. baumannii**
  - Predominantly in Southern Europe and Southeast Asia (up to 15-40%)
  - Hetero-resistance: 18.7% to 100%
  - SENTRY (2006-2009): 0.9-3.3% (Korea, 30.6%)
  - China (2009-2014): 3%
  - Greece (2014): 7.9%

Summary

- Emerging threats of colistin resistance in Gram-negative bacteria
  - *mcr* genes continue to spread among Enterobacteriaceae and will diffuse in non-fermenters such as *P. aeruginosa* and *A. baumannii*?

- Actions:
  - Polymyxins are banned as growth promoters and for prophylaxis in animals
  - Rational use of colistin is audited in hospitals
  - Carriers or patients infected with isolates harbouring both *mcr*-1 and carbapenemase genes are strictly isolated
  - Targeted surveillance plus molecular epidemiology is performed in hospitals

30th TAIPEI ICC 2017 TAIWAN
24 – 27 NOVEMBER 2017
INTERNATIONAL CONGRESS OF CHEMOTHERAPY AND INFECTION 2017
Venue: Taipei International Convention Center

Save the Date
Abstract Submission Opens November 2016

www.icc2017.tw