One Health and the control and prevention of antimicrobial resistance: Perspectives from human medicine

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VA Pittsburgh Healthcare System
Director, XDR Pathogen Lab and Mycology Research Unit
University of Pittsburgh

One Health, One Planet 2019
Phipps Conservatory and Botanical Gardens
Pittsburgh, PA
14 March 2019
65 y/o woman; double lung transplant for COPD.

Fever; shortness of breath. On admission required ventilation.

An illustrative case, 2019

**TREATMENT**

- Meropenem
- Ceftazidime-avibactam
- Meropenem
- Meropenem + Gentamicin

**LAB RESULT**

- C-R *K. pneumoniae*
- 2 types of ESBL *K. pneumoniae*
- ESBL *K. pneumoniae*
- C-R & ESBL *K. pneumoniae*
The rise of CRE* superbugs

Two More Hospitals Report ‘Superbugs’ on Endoscopes

By MAGGIE FOX

Hospitals Plagued by Unbeatable ‘Superbugs’

*Carbapenem Resistant Enterobacteriaceae
The rise of CRE* superbugs

NBC NEWS
HEALTH
MAR 5, 2015, 12:27 AM ET

Two More Hospitals Report ‘Superbugs’ on Endoscopes
By MAGGIE FOX

Hospitals Plagued by Unbeatable ‘Superbugs’
"USA TODAY" FINDS THOUSANDS OF CASES IN RECENT YEARS
(NEW/RE) - US hospitals are quietly fighting an incredibly high stakes war that they look unlikely to win against "superbugs" that resist even the most potent antibiotics available, a USA Today investigation has concluded. The paper has compiled evidence showing that hospitals across the country have seen thousands of infections from... More »

*Carbapenem Resistant Enterobacteriaceae
The rise of CRE* superbugs

10 million deaths due to drug-resistant infections per year in 2050

*Carbapenem Resistant Enterobacteriaceae
An illustrative case, 2019

65 y/o woman; double lung transplant for COPD. Fever; shortness of breath. On admission required ventilation.

Pneumonia

DAY

0 10 20 30 40 50 60

Septic shock
Altered mental status

C-R K. pneumoniae

2 types of ESBL K. pneumoniae

$728,035

DAY 25

DAY 54

CT B
An illustrative case, 2019

65 y/o woman; double lung transplant for COPD. Fever; shortness of breath. On admission required ventilation.

Lost global production due to antimicrobial resistance 2016-2050: $100 trillion

Review on Antimicrobial Resistance, Wellcome Trust and UK Department of Health
Antibiotic resistance threats

<table>
<thead>
<tr>
<th>Urgent Threats</th>
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<tbody>
<tr>
<td><em>Clostridium difficile</em></td>
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<tr>
<td>Carabapenem-resistant Enterobacteriaceae</td>
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<tr>
<td><em>Neisseria gonorrhoeae</em></td>
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<tr>
<th>Serious Threats</th>
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<tbody>
<tr>
<td>Multidrug-resistant <em>Acinetobacter</em></td>
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<tr>
<td>Drug-resistant <em>Campylobacter</em></td>
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<tr>
<td>Fluconazole-resistant <em>Candida</em></td>
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<tr>
<td>Extended spectrum Enterobacteriaceae</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Enterococcus</em></td>
</tr>
<tr>
<td>Multidrug-resistant <em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>Drug-resistant non-typhoidal <em>Salmonella</em></td>
</tr>
<tr>
<td>Drug-resistant <em>Salmonella</em> serotype <em>Typhi</em></td>
</tr>
<tr>
<td>Drug-resistant <em>Shigella</em></td>
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<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
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<tr>
<td>Drug-resistant <em>Streptococcus pneumoniae</em></td>
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<tr>
<td>Drug-resistant tuberculosis</td>
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<th>Concerning Threats</th>
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<tbody>
<tr>
<td>Vancomycin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Erythromycin-resistant Group A <em>Streptococcus</em></td>
</tr>
<tr>
<td>Clindamycin-resistant Group B <em>Streptococcus</em></td>
</tr>
</tbody>
</table>

Table 2. US Centers for Disease Control and Prevention list of the greatest drug-resistant microbial threats in the United States.

History of penicillin resistance

“... the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism.”
26 June, 1945
“Surveys of hospitals have found that practices to improve antimicrobial use are frequently inadequate and not routinely implemented”
“Surveys of hospitals have found that practices to improve antimicrobial use are frequently inadequate and not routinely implemented”
Mandates for Antimicrobial Stewardship (AMS)

CDC Core Elements of AMS
- Hospitals
- Nursing homes
- Outpatient
Core elements of AMS programs

- **Leadership commitment**
  - Human, financial, IT resources
- **Accountability**
  - Single leader (M.D.) responsible for program outcomes
- **Drug expertise**
  - Single leader (Pharmacist) responsible for improved antibiotic use
- **Action**
  - Implementing at least one recommended action
- **Tracking**
  - Monitoring prescribing and resistance
- **Reporting**
  - Regular reporting on antibiotic use and resistance
- **Education**
  - Optimal prescribing and resistance

E. Friestrom, E. McCreary
Core AMS team

“There is no single template for a program to optimize antibiotic prescribing”
Does AMS work?

- 38 studies, 6 AMS intervention types
- Reduced utilization (11%-38%), lowered costs (US$5-10/patient-day), shortened duration of treatment, reduced inappropriate use and adverse events/toxicity
- Not associated with increased nosocomial infection rates, lengths of stay, or mortality
- Interventions beyond >6 mos were associated with reduced resistance
AMS: Still a lot of work to do

Baseline (Jan - Apr 2016) vs Intervention (Jan - Apr 2017) vs Post-Intervention (Jan - Apr 2018)

- Baseline: 61.4%
- Intervention: 40.0%
- Post-Intervention: 45%

Brooke Decker, MD
AMS: Still a lot of work to do

Fluoroquinolones utilization over time

Clindamycin utilization over time

Fluoroquinolones utilization over time
 Initiation of UPMC AMS

Clindamycin utilization over time
 Initiation of UPMC AMS

UMC Presbyterian campus K. pneumoniae

UMC Presbyterian campus E. coli

M. Hong Nguyen, MD
Antibiotic Resistance in Humans and Animals
A National Academy of Medicine Perspective

Antibiotics purchased for livestock in the U.S. in 2014
15.4 million kilograms

Antibiotics purchased for humans in the U.S. in 2014
3.5 million kilograms

"Antimicrobials for livestock account for 80% of the antimicrobials purchased in the United States. To pretend that we can address antibiotic resistance that results from antimicrobial use by focusing on the 20% that occurs in humans and ignoring the 80% that occurs in animals is to fail as a society. We have a crisis of antibiotic resistance."
Antibiotic resistance: World on cusp of 'post-antibiotic era'

By James Gallagher
Health editor, BBC News website
19 November 2015
One Health AMR Case Study 1: Colistin

Antibiotic resistance: World on cusp of 'post-antibiotic era'
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Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

Published Online
November 18, 2015
http://dx.doi.org/10.1016/S1473-3099(15)00424-7
Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections

Matthew E. Falagas\textsuperscript{1,2,3} and Sofia K. Kasiakou\textsuperscript{1}

\textsuperscript{1}Alfa Institute of Biomedical Sciences (AIBS) and \textsuperscript{2}Department of Medicine, "Henry Dunant" Hospital, Athens, Greece; and \textsuperscript{3}Tufts University School of Medicine, Boston, Massachusetts
China, Brazil, Europe (certain countries)
- Administered orally to pigs, poultry, calves for treatment, prophylaxis, metaphylaxis of diarrhea, and/or as growth promoter
- Vastly exceeds use in humans (12,000 tonnes in China)

Phenotypic resistance testing is technically difficult
- Not included in routine surveillance of animals, environment, food, humans
Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Bao lei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

![Figure 2: Map of China](image)

<table>
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<tr>
<th>Escherichia coli</th>
<th>Year</th>
<th>Positive isolates (%)</th>
<th>number of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigs at slaughter</td>
<td>All</td>
<td>166 (20.6%)</td>
<td>804</td>
</tr>
<tr>
<td>Pigs at slaughter</td>
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<td>268</td>
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<tr>
<td>Pigs at slaughter</td>
<td>2014</td>
<td>67 (20.9%)</td>
<td>320</td>
</tr>
<tr>
<td>Retail meat</td>
<td>All</td>
<td>78 (14.9%)</td>
<td>523</td>
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<td>130</td>
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<tr>
<td>Inpatient</td>
<td>2014</td>
<td>13 (1.4%)</td>
<td>902</td>
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| Klebsiella pneumoniae           | Inpatient | 3 (0.7%) | 420 |

Table 2: Prevalence of colistin resistance gene mcr-1 by origin
Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohel Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

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| **Klebsiella pneumoniae**                   |                                        |
| Inpatient                                  | 3 (0.7%)/420                            |

Figure 2: Structure of plasmid pHKHP45 carrying mcr-1 from Escherichia coli strain SHP45
CRE: Our last line of defense is breached

2015

Q4

First report of transmissible colistin mcr-1 resistance gene

2016

Q1

Mcr-1 resistance plasmid found in carbapenem-resistant Enterobacteriaceae

Q2

Mcr-1 found in CRE + NDM-9 E. coli

Q3

MDR E. coli harboring mcr-1 and bla

First human case in US

Second US case reported in June

Five new mcr-like genes have arisen globally: mcr-2 through mcr-5, icr-Mo

Bloomberg.

AAC 2016 May 26 online; doi:10.1128/AAC.01103-16
Case Study 2: Azole-R Aspergillus
Case Study 2: Azole-R Aspergillus

Azole antifungals

Chowdhary Plos Pathogens 2013
Case Study 2: Azole-R Aspergillus

Azole antifungals
Crop protection, wood preservation, fruit and vegetable mildew and rust

Chowdhary Plos Pathogens 2013
Case Study 2: Azole-R Aspergillus

>25% clinical isolates azole-R in the Netherlands

~2-6% in U.S.

TR$_{34}$/L98H mutation
Case Study 3: AMS in the poultry industry

• Ceftiofur was administered to eggs or day-old hatchery chicks as prophylaxis against *E. coli* or egg yolk infections
  – Canadian Integrated Program for Antimicrobial Resistance Surveillance
    • High rates of ceftiofur resistant *Salmonella*
    • Ceftriaxone cross-resistance

McEwen, Microbiol Spectrum 2017; CPIARS 2009
Case Study 3: AMS in the poultry industry

McEwen, Microbiol Spectrum 2017; CIPARS 2009
Case Study 3: AMS in the poultry industry

• Japan, 2012
  – Voluntary withdrawal of ceftiofur use in hatcheries
    • Decrease in cephalosporin-R *E. coli* in broilers

• Canada, 2014
  – Ceftiofur voluntary ban by Canadian poultry industry

• Europe
  – Label claim for ceftiofur use in day-old chicks withdrawn

• U.S.
  – Off-label use of 3rd generation cephalosporin banned

McEwen, Microbiol Spectrum 2017
One Health strategies against AMR

- Drug classification
  - Limit use of medically important antibiotics

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<thead>
<tr>
<th>Category</th>
<th>Human health (WHO)</th>
<th>Animal health (OIE)</th>
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<tbody>
<tr>
<td>Critically Important</td>
<td>Aminoglycosides, Ansamycins, Carbapenems and other penems, Cephalosporins (3rd and 4th generation), Phosphonic acid derivatives, Glycopeptides, Glycylcylines, Lipopeptides, Macrolides and ketolides, Monobactams, Oxazolidiones, Penicillins (natural, aminopenicillins, and antipseudomonal), Polymyxins, Quinolones, Drugs used solely to treat tuberculosis or other mycobacterial diseases</td>
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<td></td>
<td>Aminoglycosides, Amphenicol, Cephalosporins (3rd and 4th generation), Macrolides, Penicillins (natural, aminopenicillins, aminopenicillins with beta-lactamase inhibitor, antistaphylococcal), Fluoroquinolones, Sulfonamides, Diaminopyrimidines, Tetracyclines</td>
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</tr>
<tr>
<td>Highly Important</td>
<td>Ampicillin, Ampicillicins, Cephalosporins (1st and 2nd generation) and cephapemycins, Lincosamides, Penicillins (antistaphylococcal), Peumomultins, Pseudomonic acids, Rimphenazines, Steroid antibacterials, Streptomyciniosides, Sulphonamides, dihydrofolate reductase inhibitors, and combinations, Tetracyclines</td>
<td></td>
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<tr>
<td></td>
<td>Ansamycin—rifamycins, Cephalosporins (1st and 2nd generation), Ironophores, Lincosamides, Phosphonic acid, Peumomultins, Polymyxins (including bacitracin and other polypeptides), 1st-generation quinolones (flumequin, miloxacin, nalidixic acid, oxolinic acid)</td>
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<tr>
<td>Important</td>
<td>Aminocyclids, Cyclic polypeptides, Nitrofurantoin, Nitroimidazoles</td>
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<tr>
<td></td>
<td>Aminocoumarin, Arsenical, Bicyclomycin, Fusidic acid, Orthosomycins, Quinonines, Streptomyciniosides, Tetracyclines</td>
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One Health strategies against AMR

• AMS
  – Align medical, animal, agricultural activities
  – Regulatory
    • Antimicrobials in animal growth promotion
    • Extra-label fluoroquinolone, 3rd generation cephalosporin use in animals
    • Prescription-only antibiotics for veterinary use

• Surveillance and research

• Improved sanitation, hygiene and infection prevention

• New therapeutics, diagnostic tests, vaccines
One Health strategies against AMR

• Communication, education, and training
  – Views on moral implications of antibiotic use
    • Physicians, Veterinarians
      – Limit inappropriate use and resistance ("do no harm")
    • Poultry industry leaders
      – Responsibility to business and employees
  – Interviews with farmers in India indicated that antibiotics are viewed as vitamins and feed supplements
One Health strategies against AMR

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• Human medicine needs to get its own house in order
Acknowledgments

UPMC AMS and XDR Pathogen Lab
VAPHS AMS

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- Deanna Buehrle PharmD
- Jae Hong, MD

UPMC

VAPHS

VA Pittsburgh Healthcare System
Worldwide emergence of fungal disease and antifungal-R

Fisher, Science 2018