Effective Scientific Advances and Promising Research to Reduce the Need for Antimicrobials: Human Health Perspective

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National Academy of Sciences, Engineering, Medicine:
Combating Antimicrobial Resistance

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Disclosures

- No relevant financial disclosures
- For a complete list and description of CDC Foundation-funded projects in which DHQP participates, see http://www.cdcfoundation.org/what/programs/list
- The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
New Drugs Alone Aren’t Enough to Protect Americans

Combating AR requires comprehensive, aggressive action across the U.S. gov’t and around the globe
CDC’s Approach to Combat Antibiotic Resistance Includes Innovation

Connecting the dots to address current and future gaps and opportunities

Ongoing innovation for new strategies for prevention:
- Patient-level interventions
- Healthcare facility interventions
- Regional interventions
CDC’s Approach to Combat Antibiotic Resistance Includes Innovation

Discovering, investigating, and implementing new solutions to protect Americans

Academic & Healthcare Partners
- 28 collaboratives discovering new ways to protect patients and scale up effective interventions across health systems
- 11 Prevention Epicenters identifying new prevention strategies to guide clinical practice and maximize public health impact
- 14 studies exploring the gut-drug relationship and the patient’s microbiome
- 260 white papers submitted to CDC’s recent Broad Agency Agreement solicitation

Industry Partners
- With the CDC-FDA AR Isolate Bank, supporting development of new drugs and diagnostics with 46,000 isolates and more than 500 orders
- Making public CDC’s sequencing data from AR pathogens to spur innovation, research
A Quick Overview of the Microbiome – Role in AR

- Research on the microbiome is a central component to drive innovations that will protect patients.
- The microbiome is a community of germs in and on your body (e.g., skin, gut, oral and respiratory systems, urogenital tract).
- A healthy microbiome helps protect you from infection.
  - “Antibiotic pressure” = pressure on the microbiome

*Image used with permission from www.BryanChristieDesign.com*

*Remember: You don’t become resistant to antibiotics, but the bacteria in and on your body can.*
Antibiotics disrupt your microbiome, wiping out both good and bad bacteria. Resistant bacteria—like MRSA, CRE, and C. difficile—can take advantage of this disruption and multiply.

A healthy microbiome helps protect you from infection. Improved antibiotic use and a healthy microbiome can keep us and our communities well.

With this overgrowth, your body is primed for infection. Once colonized, you can easily spread the resistant bacteria with others.
Key Premise

- The intact human microbiome is a primary host defense for preventing colonization, dominance, transmission, and infection with opportunists or pathobionts
  - Clostridium difficile
  - Multidrug-resistant organisms (VRE, CRE, ESBLs, others)
  - Salmonella, Shigella, and Campylobacter spp.

- Why ‘Pathobiont’?
  - Commensal: low virulence
  - Opportunist~pathobiont: emphasizes necessity of microbiome disruption in virulence
  - Pathogen: high virulence
Colonization Resistance

CDC Developing Microbiome Indices (MIs)

- Clinical Medicine and Public Health
  - Monitor patients before, during, and after antibiotic therapy
  - Alert when disruption reaches critical level that promotes colonization, dominance, infection, or transmission
  - Stage patient need for microbiome restoration

- Characterize risk of specific antibiotics and other disruptive agents
  - Rating system to gauge relative risks of different agents—aid in drug development
  - Future: MDIs determined during approval process and included in package insert—surrogate outcome for AR outcomes

- Microbiome protectants (i.e. inactivate or bind antibiotic) or restoratives (i.e. FMT or probiotics)
  - Maintaining or improving microbiome status to reduce AR outcomes
Conceptualizing Microbiome Indices (MIs) for Drug Development, Clinical Medicine, and Public Health

What is the usual MDI seen with antimicrobial X?

- Antibiotic disruption
- Multidrug Resistant Organism*
- Further Antibiotic disruption

Normal microbiome: Resistant to colonization
Disrupted microbiome: Susceptible to colonization
Colonization
Overgrowth and Dominance

Cross Transmission

What is the cumulative MDI that leads to transmission?

What is the MDI permissive for colonization?

*Examples include carbapenem-resistant enterobacteriaceae, vancomycin-resistant enterococci, extended-spectrum beta-lactamase producing enterobacteriaceae. May also include transfer of genetic transfer of resistance determinants
Improve Use: Applied Research to Protect the Microbiome & Antibiotics

- Predict impact of new and old antibiotics on the microbiome, determine risk of disruption (i.e. determine each antibiotic’s specific disruptive potential)
- Determine how to tailor antibiotic stewardship to a patient’s microbiome and/or to a specific population of patients (e.g., hospital unit, doctor’s office)
- Develop and test microbiome diagnostics and protocols:
  - Develop diagnostics that will measure and monitor a patient’s risk for colonization, transmission, and infection.
  - Use microbiome or metabolome to assist with diagnosis of infection
- Support development of therapeutics that will restore and protect the microbiome when antibiotics must be used
Example: Reducing Resistance in Hematopoietic Stem Cell Transplant Patients through FMT

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Negative rectal swab at 1 week</th>
<th>Decolonization at 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All No.</td>
<td>Antibiotics (-) No.</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDM1+</td>
<td>8/14 57</td>
<td>6/6 100</td>
</tr>
<tr>
<td>Other, carbapenem-resistant</td>
<td>2/3 67</td>
<td>2/2 100</td>
</tr>
<tr>
<td>ESBL+</td>
<td>1/2 50</td>
<td>0/1 0</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESBL+</td>
<td>11/11 100</td>
<td>3/3 100</td>
</tr>
<tr>
<td>OXA-48+</td>
<td>1/1 100</td>
<td>1/1 100</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBL+</td>
<td>2/2 100</td>
<td>2/2 100</td>
</tr>
<tr>
<td>Other, carbapenem-resistant</td>
<td>1/2 50</td>
<td>1/2 50</td>
</tr>
<tr>
<td>Carbapenem-resistant <em>Enterobacter cloacae</em></td>
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<td>1/2 50</td>
</tr>
<tr>
<td>Vancomycin-resistant enterococci (VRE)</td>
<td>2/2 100</td>
<td>1/1 100</td>
</tr>
<tr>
<td><strong>Acinetobacter ursingii MBL+</strong></td>
<td>1/1 100</td>
<td>1/1 100</td>
</tr>
<tr>
<td><strong>Stenotrophomonas maltophilia</strong></td>
<td>1/1 100</td>
<td>1/1 100</td>
</tr>
</tbody>
</table>


Belinski et al. Clin Infect Dis 2017
Phage Therapy

- Quickly cleared from bloodstream
- Promise for treating chronic infections involving biofilms
  - Phagoburn—cocktail against *E. coli* and *P. aeruginosa*
  - AmpliPhi—*S. aureus*
  - Technophage—Diabetic foot ulcers
- Microbiome remediation
  - Role of phage in FMT
Phage to Address Antibiotic Resistance in Device and Environmental Biofilms

- CDC biofilm lab has previously tested phage on central venous and urinary catheters
- CDC response to CRE outbreaks
  - Sink drain (P-traps) and toilet contamination
  - Clonal, plasmid, and transposon outbreaks
- Very difficult to eradicate
- Practical steps: covers on hoppers
- CDC intramural innovation
  - ‘Sink gallery’
  - Testing phage in drains

Kotay S....Mathers A. Appl Environ Microbiol. 2017 Mar 31;83(8).
What Could it Look Like in Practice?
Together, Innovations Preventing CRE Infections

- **Microbiome susceptibility**
  - Develop MDIs that predict risk for colonization and infection
  - Novel protection and restoration strategies
  - Improving implementation of antibiotic stewardship to reduce unnecessary exposures that cause cumulative microbiome disruptions that lead to colonization and infection

- **Transmission**
  - Whole genome sequencing (and metagenomics) to understand transmission dynamics, from horizontal gene transmission in an individual patient’s microbiome, to plasmid and strain transmission within a facility (LTACH) or across the nation
  - Understand and mitigate environmental reservoirs (sink drains, hoppers, sewage)
  - Innovative strategies to improve overall effectiveness of contact precautions
  - Developing and testing regional interventions that leverage knowledge of patient-sharing networks and cluster detection to prevent inter-facility spread
CDC & FDA AR Isolate Bank: Sharing Bug Data to Support Drug, Diagnostic Development

CDC gathers resistant bacteria through surveillance/outbreak programs.

CDC analyzes the bacteria’s resistance & shares with researchers.

Currently includes 496 isolates (on 14 panels).

Since July 2015, CDC has processed 516 orders (more than 46k isolates).

New diagnostic tests & antibiotic drugs are developed using the bacteria & data.

Helping healthcare providers know that the tests they use and drugs they prescribe will protect patients.

www.cdc.gov/DrugResistance/Resistance-Bank
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