Microbiome for Gut Health: A modern tool and a target in the effort to address AMR

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Disclosure

- NO financial disclosure
- My presentation should not directly reflect the opinions of the following committees I serve:
  - HKU-AMR Working Group
  - Scientific Steering Committee of Institut Pasteur International Network (COS-RIIP)
  - klebNET International Network
Microbial World

- $5 \times 10^{30}$ bacteria on Earth

Whitman et al. 1998. PNAS 95:6578
## Microbes in Animals

Whitman et al. 1998. PNAS 95:6578

### Table 4. Total number of prokaryotes in some representative animals

<table>
<thead>
<tr>
<th>Animal</th>
<th>Organ</th>
<th>Cells/ml or cells/g</th>
<th>Organ contents*</th>
<th>No. of animals†</th>
<th>No. of cells, × 10^{23}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Colon</td>
<td>3.2 × 10^{11}</td>
<td>220 g</td>
<td>5.6 × 10^{9}</td>
<td>3.9</td>
</tr>
<tr>
<td>Cattle</td>
<td>Rumen</td>
<td>2.1 × 10^{10}</td>
<td>106 liter</td>
<td>1.3 × 10^{9}</td>
<td>29.0</td>
</tr>
<tr>
<td>Sheep and goats</td>
<td>Rumen</td>
<td>4.4 × 10^{10}</td>
<td>12 liter</td>
<td>1.7 × 10^{9}</td>
<td>9.0</td>
</tr>
<tr>
<td>Pigs</td>
<td>Colon</td>
<td>5.4 × 10^{10}‡</td>
<td>9 liter</td>
<td>8.8 × 10^{8}</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>Cecum</td>
<td>2.8 × 10^{10}‡</td>
<td>1 liter</td>
<td>8.8 × 10^{8}</td>
<td>0.3</td>
</tr>
<tr>
<td>Domestic birds§</td>
<td>Cecum</td>
<td>9.5 × 10^{10}</td>
<td>2 g</td>
<td>1.3 × 10^{10}</td>
<td>0.024</td>
</tr>
<tr>
<td>Termites</td>
<td>Hindgut</td>
<td>2.7 × 10^{6}¶</td>
<td></td>
<td>2.4 × 10^{17}</td>
<td>6.5</td>
</tr>
</tbody>
</table>

*Organ contents in grams or liters
†Number of animals
‡Additional data available
§Data not available
¶Data not applicable
Functions of Human Gut Microbiome

**MAKE**
vitamins, including
B12, K and FOLATE

**DEFEND**
against harmful
MICROORGANISMS

**TEACH**
the immune system
to tell friends from foes

**INFLUENCE**
the calories you harvest

**PRODUCE**
important molecules
that travel around the body

**HELP**
produce serotonin, important for optimal
gut function
Investing In Microbiome – A Look Back Into The Future
Gut Microbiota-Associated Diseases

Gut-brain axis, mental diseases and behavior
Restoring Healthy Gut Microbiome

- Fecal Microbiome Transplant (FMT)
- Engineered Consortia
- Antibiotics
- Prebiotics
- Probiotics
- Peptides
- Phage Therapy
- Bioactive compounds
- Postbiotics
- Microbial Enzymes

Diagram:
- Diseased state vs. Healthy state
- Metagenome alteration
- Metabonome alteration
- Disease-associated metabolite profile
- Relative health status
Discovery of Antibiotics

Sir Alexander Fleming (1881-1955)
Collateral Damage Of Antibiotic Use?

Collateral Damage Of Antibiotic Use?

Prof. Martin J. Blaser
Rutgers University

Obesity in Human vs Livestock Animals
Another Collateral Damage Of Antibiotic Use?

The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

~Alexander Fleming
Post-antibiotic Era

Lord Jim O'Neill's Review on AMR
Causes of AMR

- Over-prescribing of antibiotics
- Patients not finishing their treatment
- Over-use of antibiotics in livestock and fish farming
- Poor infection control in hospitals and clinics
- Lack of hygiene and poor sanitation
- Lack of new antibiotics being developed

[WHO infographic for antibiotic resistance]
Impact of Early-life Antibiotic Exposure on Gut Microbiome

Tun et al. Unpublished data
Impact of Early-life Antibiotic Exposure on Gut Resistome

Cluster dendogram for the infant gut resistome (Using Bray Curtis Distance)

Tun et al. Unpublished data
Antibiotic-mediated changes in the fecal microbiome of broiler chickens define the incidence of antibiotic resistance genes

Wenguang Xiong1,2, Yulin Wang2, Yongxue Sun1, Liping Ma3, Qinglin Zeng1, Xiaotao Jiang2, Andong Li2, Zhenling Zeng1* and Tong Zhang2*
Microbiome and Resistome of Day-old chicks (DOCs)

Zhang et al. Unpublished data
Association between Gut Dysbiosis and AMR Acquisition???

- No strong scientific evidence has been reported.
- Thus, we tested the question in our Prospective Cohort of Hong Kong Travelers.

Travel-associate risk factors

Poonsuk et al. 2019. Travel Med Infect Dis. Under Review
Flow chart of study design

Inclusion criteria: Hong Kong travelers (≥18 years) who travel abroad for a minimum of one night stay
Association between gut microbiome diversity and AMR

Loss of species richness/diversity of gut microbiome is associated with AMR acquisition.

Liang & Poonsuk et al. Unpublished data
What are the alternatives to antibiotics (ATA) left for us?

- Fecal Microbiome Transplant (FMT)
- Engineered Consortia
- Probiotics
- Prebiotics
- Antibiotics
- Peptides
- Phage Therapy
- Bioactive compounds
- Postbiotics
- Microbial Enzymes
Fecal Microbiome Transplant (FMT) in the History

- **4th Century (Ge Hong):**
  - Oral human fecal suspension ("yellow soup") for severe diarrheal illnesses, food poisoning

- **16th Century (Li Shinzen):** fermented fecal solution, dry feces - treated fever, severe diarrhea, vomiting and constipation

- **17th Century:** Veterinary medicine
  - Fecal transfer for horses with diarrhea

- **1958:** FMT enema
  - Eismann, et al. 4 patients with pseudomembranous colitis
  - “Dramatic” response within 48 hours
Current FMT Delivery Methods

- Gastroscopy
- Nasoenteric tubes
- Colonoscopy
- Enema

Traditional FMT Delivery

- Oral Capsule
- Fresh
- Frozen
- Lyophilized

- Bile absorbent resins
- Water-in-oil emulsion
- Double or triple encapsulation
- Vcaps™ HPMC capsules
- Layer-by-layer encapsulation

Genetic engineering
Fecal Microbiome Transplant (FMT)

- Successfully used to treat recurrent *C. difficile* infection.
- Use in other GI disorders and extra-GI diseases are underway.
- Several barriers remain:
  - Characteristics of Healthy Microbiome?
  - Long-term safety of the recipient
  - Donor selection
  - Need high quality control
  - Inconsistencies among different studies
3 unresolved issues in FMT!

- Transplants should be adequately screened for potentially harmful bacteria. These should include virulence factors and resistance genes. The screening procedures also need to be continuously updated as new resistance genes or virulence factors are identified.

- Patients should be adequately informed about the procedure and the risks involved, especially the most vulnerable patients. The transplants are complex mixtures of bacteria that we still only know a fraction about.

- Appropriate patient groups need to be identified. Are there comorbidities that affect the safety of fecal microbiota transplants?
Use of FMT in Livestock - Need Caution!!
What are the alternatives to antibiotics (ATA) left for us?

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- Postbiotics
- Microbial Enzymes
Impact of xylanases on gut microbiota of growing pigs fed corn- or wheat-based diets

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b Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, MB, R3T 2N2, Canada
c Department of Animal Bioscience, University of Guelph, Guelph, ON, N1G 2W1, Canada

Table 1
Effects of different xylanase supplementations within basal diets on the apparent total tract digestibility of nutrients and VFA concentrations in the ileal and cecal digesta of piglets.1

<table>
<thead>
<tr>
<th>Item</th>
<th>Corn-based diet a</th>
<th>Wheat-based diet a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>XA</td>
</tr>
<tr>
<td>Digestibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>71.04</td>
<td>73.26</td>
</tr>
<tr>
<td>GE</td>
<td>71.01</td>
<td>72.89</td>
</tr>
<tr>
<td>CP</td>
<td>70.98</td>
<td>73.78</td>
</tr>
<tr>
<td>Fat</td>
<td>50.29</td>
<td>58.30</td>
</tr>
<tr>
<td>VFA concentration, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td>10.66</td>
<td>10.31</td>
</tr>
<tr>
<td>Cecum</td>
<td>42.75</td>
<td>46.80</td>
</tr>
</tbody>
</table>

SEM = standard error of the mean.

a, b Mean values within a row with different superscripts were significantly different (P < 0.05).
1 Reported values are least-squares means.
2 The basal diets were supplemented with or without 75 mg/kg of 1 of 5 types of xylanase supplements (xylanase A [XA], xylanase B [XB], xylanase C [X], xylanase D [XD], and xylanase E [XE]) from various original microorganisms.
Take Home Messages

- Due to increasing awareness of AMR globally, we need to explore more about ATA for both human and animals.

- Optimizing gut health/microbiome is most desirable to maintain health and production in livestock agriculture.

- More scientific investigations are needed to build evidences for the choices of ATA.

- International organizations and scientific communities should develop regulations and recommendations to benchmark ATA available in the market.
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