Antibiotic use and the gut microbiota: damage control

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Presenter disclosure

- I am co-founder and CSO of Nubiyota LLC, a company founded to commercialize Microbial Ecosystem Therapeutics, which I will mention in this talk
We are not human!

We are *super-organisms* of human and microbial cells
We exist in a delicate host: microbe equilibrium
How human are we?

• ‘Reference human'
  • 70 kilograms, 20–30 years old, 1.7 metres tall
• ~30 trillion human cells
• 39 trillion bacterial cells

\[
\frac{\text{Human}}{\text{Bacteria}} = 1 : 1.3
\]

Sender, Fuchs and Milo
doi: https://doi.org/10.1101/036103
Most of these microbes live in our gut

The gut microbiome

- Each gram of feces contains $\sim 10^{11}$ bacterial cells
  - $\sim 200$ species

That’s 10 trillion cells in the average bowel movement!
Everyone is different

Gut microbial ecosystems are highly variable in composition and abundance profiles between people
Ecosystem biodiversity drives overall health

High diversity of species:
- Healthy ecosystem
- Balance
- Functional redundancy
  - High gene count
- Resistance to damage

Low diversity of species:
- Sick ecosystem
- Imbalance
- Functional disability
  - Low gene count
- Susceptibility to damage

This is also true at the microbial scale
Remarkably...

The bacterial community in your gut remains stable from

• weaning…
• …to old age

And we are only just starting to understand this homeostasis
How do we acquire our microbes?

- Vaginal Delivery
- Breastfeeding
- Interaction with environment

Progressive microbial colonization

Toh & Allen-Vercoe, MEHD Feb 2015
How do we acquire our microbes?

- Vaginal Delivery
- Breastfeeding
- Interaction with environment

- C-section Delivery
- Maternal Antibiotics
- Formula feeding
- Indoor living
- Excessive sanitation
- Chemical preservation of food

Toh & Allen-Vercoe, MEHD Feb 2015
What do our gut microbes do for us?

• Immune system regulation
• Calorie extraction from foods
• Crowd out potential pathogens
• Make some vitamins and cofactors
• Improve intestinal function
• Remove toxins and carcinogens

• As important to us as a liver
  • A virtual organ
Our microbes are vitally important…

• But we are working very hard to exterminate them!
Are we damaging our health by eroding microbiome diversity?

• **Hygiene hypothesis** (Strachan, 1989)
  • Lack of exposure to certain infectious agents during childhood drives allergic disease

• **Old friends hypothesis** (Rook, 2003)
  • Humans are dependent on a co-evolved microbiome to educate the immune system and prevent inflammatory disease

• **Missing microbiota hypothesis** (Blaser & Falkow, 2009)
  • Loss of microbiota generally compounds over generations, and *recent changes in lifestyle* have greatly exacerbated this loss
Many studies have shown:

- Gut microbiota changes significantly with antibiotic use
- Takes a long time afterwards to return to baseline
- Sometimes does not return to baseline at all
- Repeated ‘hits’ cause vast changes from which the ecosystem does not recover

The average person in the U.S. will receive 10-20 courses of antibiotics by the time he or she is 18 years old.
Examples of diseases associated with reduced gut microbiota diversity
(published research)

- Infant colic
- Autism
- Allergic asthma
- Irritable Bowel Syndrome
- Eczema
- Colorectal cancer
- Celiac disease
- Obesity
- Neonatal necrotizing enterocolitis
- Clostridioides difficile infection
- Inflammatory bowel diseases
- Lack of microbial diversity
- Loss of ‘keystone’ species
- Overgrowth of opportunistic pathogens
- Poor diet/lifestyle
- Drug interactions

Looking inside the black box is the key to understanding disease

"Dysbiosis"
The human gut microbiota is a complex microbial ecosystem. Its function and behaviour is best studied as a whole.
The human colon is a type of ‘bioreactor’…

…thus, bioreactors can be used to emulate the human colonic environment.
Seeded with fresh feces or defined communities and set to model the ecosystem of the colon
- Host-free system
- Can be used to ‘culture the unculturable’
- Can support whole gut microbial ecosystems for several weeks at a time

We can model the gut microbiota under different stress conditions
- We can try to protect against the effects of stress
When most people think of gut microbes, they think of the good and the bad...

**The Good**
- Lactic Acid Bacteria (LAB)
  - E.g. *Bifidobacterium* and *Lactobacillus* spp.
- Butyrate-producing bacteria
  - E.g. *Faecalibacterium prausnitzii*, *Roseburia* spp.

**The Bad**
- Opportunistic pathogens
  - *E. coli*
  - *Clostridioides difficile*
  - *Bacteroides fragilis*
- Sulfate-reducing bacteria
  - E.g. *Desulfovibrio* spp.

**The Ugly**: it really is not that clear-cut!
Some microbes are like bad teenagers in a subway station…

In a crowded environment they tend to behave well.

When the crowds are gone, they tend to start behaving in antisocial ways.
Fixing dysbiosis with probiotics

• If you take an antibiotic, you can just cancel the negative effects out by using a probiotic, right?
  • Nope!

• Many types and strains of probiotics
• Many manufacturers, some legitimate, most not
• Many over-inflated claims
• Very little actual science

From a typical probiotic website: “There are over 500 different types of bacteria in the digestive system; the two most prevalent are Lactobacilli and Bifidobacterium. Bifidobacterium are the most prevalent bacteria in the large intestine, while Lactobacilli are the most prevalent in the small intestine. As we age, studies show the levels of Bifidobacterium decline, while harmful pathogenic bacteria increase. This is one of the main reasons that intestinal ailments increase as we age.”
The layperson's view of probiotics...

Myth 1: Probiotics found in food are the same kinds of species that are found in the gut.

Myth 2: Probiotics colonize the gut.
The microbial ecologist’s view of probiotics

Normal gut microbiota
Colon: 100 billion to 1 trillion cells per gram of poop

VS.

Probiotic
2-15 billion cells per capsule
My advice: do careful research or consult reputable sources for info
http://www.probioticchart.ca/

Clinical Guide to PROBIOTIC SUPPLEMENTS
AVAILABLE IN CANADA: 2015 Edition
Indications, Dosage Forms, and Clinical Evidence to Date

Author: Dragana Skokovic-Sunjic BScPhm RPh NCMP

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Dr. John Marshall MD MSc FRCP C AGAF, Dr. Tom Smiley BScPhm PharmD

Medical Editor: Ivana Sunjic BSc

Download for free PROBIOTIC mobile app
Prebiotics

• ‘Food’ for your gut microbes
• Typically non-digestible* fibre compounds
  • *your microbes digest them just fine!
• Not a one-size-fits-all approach
  • But sold that way!
  • No simple solution – fibre supplements not diverse enough
  • Could be used more cleverly
• Are we entering the era of matching foods to gut microbiota ‘types’?
• How do we do that?
**C. difficile infection: a man-made disease**

- **Normal colon**
  - *C. difficile* absent or numbers low

- **Antibiotics**
  - clindamycin
  - cephalosporins
  - ampicillin

- **Reduction in normal gut microbes**
  - *C. difficile* grows to high numbers

- **Symptoms abate**
  - Cessation of therapy
  - Return to normal

- **Vancomycin or metronidazole**

- **Ulceration of colon**

- **Death**

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*C. Carlucci, A-V lab, 2012*
Stool substitute transplant therapy for the eradication of Clostridium difficile infection: ‘RePOOPulating’ the gut

Elaine O Petroff¹, Gregory B Gloor², Stephen J Vanner³, Scott J Weese³, David Carter⁴, Michelle C Daigneault⁵, Eric M Brown⁶, Kathleen Schroeter⁷ and Emma Allen-Vercoe⁸

• **MET-1 = 33 bacterial strains**
  - 1x100 mL dose via colonoscopy
  - Two cases of severe recurrent CDI treated
  - Both patients recovered within 48 h (and have remained C. difficile-free to date)

• Same concept as a ‘fecal transplant’

• But instead of poop, we used a complex, defined ecosystem of pure microbes
  - Logical next step

• Because it’s defined, we can monitor long-term effects
Which microbial species should be chosen?

Needs of the ecosystem:
- Stability
- Diversity
- Functionality
- Strain
- Interactivity

Needs related to commercialization:
- Cost
- Safety
- Culturability
- Reproducibility
- Integrative ability

Needs of the patient: oral delivery preferred!
# Making a better MET

<table>
<thead>
<tr>
<th>MET-1</th>
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<td>Trialed as a novel probiotic</td>
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<td>33 bacterial strains, 25 species</td>
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<td>4 bacterial phyla included</td>
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Making a better MET

<table>
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<tr>
<th>MET-1</th>
<th>MET-2</th>
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<tbody>
<tr>
<td>Trialed as a novel probiotic</td>
<td>Developed as a first-in-class biologic drug</td>
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<tr>
<td>33 bacterial strains, 25 species</td>
<td>40 bacterial strains, 40 species</td>
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<tr>
<td>4 bacterial phyla included</td>
<td>5 bacterial phyla included</td>
</tr>
<tr>
<td>Pure culture as a suspension of microbes for delivery via colonoscope</td>
<td>Pure culture as stabilized, lyophilized capsules for oral delivery</td>
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Enhanced safety

- Fecal transplants cannot be undone!
- Microbial species used for MET are confirmed generally sensitive to selected antibiotics
  - Can be removed if required
- Genomes are sequenced to check for absence of known virulence genes
- Because they are well-characterized, we can track each strain during and after treatment of a patient
Phase 1A trial currently underway

- For the treatment of recurrent *C. difficile* infection that has repeatedly failed to be resolved using antibiotic therapy
Moving towards the future:
How should we approach development of novel METs?

We need to look at the gut microbial ‘engine’

We need to look at the ‘emissions’

We need to replace the faulty parts to get the engine running optimally again
Moving towards the future:
How should we approach development of novel METs?

We need to replace missing functions to get the engine running optimally again
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