Managing microbes for health: the importance of the human gut microbiota

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Presenter disclosure

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Human health depends on microbiota health

We are super-organisms of human and microbial cells
We exist in a delicate host: microbe equilibrium
There are more bacteria living in your gut than there are people on the planet...

Gut: 200-500 bacterial species
Also Archaea as well as yeasts & other microscopic eukaryotes
Everyone is different

You have a ‘pooprint’!
Balance is important

High diversity of species:
• Healthy ecosystem
• Balance
• Functional redundancy
• Resistance to disease

Low diversity of species:
• Sick ecosystem
• Imbalance
• Functional disability
• Susceptibility to disease
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

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

Progressive microbial colonization

The window for proper gut microbiota development is narrow

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

**Metabolic**
- Fermentation of non-digestible substrates
- Production of vitamins, SCFA
- Removal of toxins, carcinogens
- Differentiation of IECs

**Structural**
- Intestinal villi and crypts
- Tight junctions
- sIgA production
- Mucus secretion

**Protective**
- Colonization resistance
- Innate and adaptive immunity
- Inflammatory cytokine oversight

**Energy**
- Competition for sites and nutrients
- Immune system and barrier function

After Cryan *et al.*
Our microbes are vitally important...

• But we are working very hard to exterminate them!
‘Extinction events’ may impact health

• Hygiene hypothesis
  – We are preventing proper colonization by being too clean

• Missing microbiota hypothesis
  – We are disturbing proper colonization across generations through e.g. antibiotic use

• Antibiotic use (especially in early childhood) may be particularly problematic
• 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.
The additional impact of the Western diet

• Average Western diet:
  • rich in refined foods,
  • low in fermented foods, complex carbohydrates, fibre

• Refined foods are easily broken down in the upper GI tract
  – Thus very little left-over food makes it to the colon

• Colon is the site of most beneficial gut microbial activity
  – Starvation of this community can lead to ecosystem damage
  – ‘extinction events’ and reduced diversity
Artificial sweeteners

...and artificial food emulsifiers

Damage your gut microbiota

Chassaing et al., doi 10.1038/nature14232, Suez et al., doi: 10.1038/nature13793
What we need to understand:

- The safety of many food additives, supplements and drugs has NEVER been assessed taking into account our microbial passengers
  – we are just scratching the tip of the iceberg
Save our Rainforests

Save our gut microbiota
Examples of diseases associated with reduced gut microbiota diversity (published research)

- Infant colic
- Autism
- Allergic asthma
- Eczema
- Celiac disease
- Colorectal cancer
- Obesity
- Neonatal necrotizing enterocolitis
- Irritable Bowel Syndrome
- Clostridium difficile infection
- 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.
Introducing ‘Robogut’

- A ‘life support’ culture system for the gut microbiota
- A ‘chemostat’ platform that mimics the colon
When you think of gut microbes, you 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*
    - *Clostridium 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 themselves

When the crowds are gone, they tend to start behaving in antisocial ways

E.g. *C. difficile*
C. difficile infection: a man-made disease

Normal colon
C. difficile absent or numbers low

Antibiotics
- clindamycin
- cephalosporins
- ampicillin

Reduction in major genera of anaerobes:
C. difficile grows to high numbers

Relapse (10-20%)

Production of exotoxins A and B

Diarrhea

Ulceration of colon

Death

Return to normal

Symptoms abate

Vancomycin or metronidazole
So, *C. difficile* is a pathogen that needs to be destroyed!

- We need to throw our best chemical weapons at it to rid ourselves of the scourge!

- ...NO, this is NOT the best strategy
A healthy gut microbiota is like a healthy lawn:
Lush growth, no room for weeds
The healthy lawn analogy

When the lawn is stressed, e.g. during drought, damage ensues
The healthy lawn analogy

If you’re unlucky, weeds can move in before the lawn recovers from the stress.
The healthy lawn analogy

Applying more damage to the lawn is one way to get rid of the weeds.
The healthy lawn analogy

Another approach is to replace the damaged turf with new, healthy growth.
How can we ‘returf’ dysfunctional gut microbial ecosystems?

Probiotics, prebiotics and beyond…
The layperson’s view of probiotics...
The microbial ecologist’s view of probiotics

Normal gut microbiota
Colon: 100 billion to 1 trillion CFU per mL

VS.
Probiotic
2-15 billion CFU per capsule
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!
  – Could be used more cleverly
• Are we entering the era of matching foods to gut microbiota ‘types’?
Fecal transplant/fecal bacteriotherapy (aka “re-turfing” or “transPOOsion”)

- Donor selected
- Usually close family member
- Screened for range of diseases that are potentially passed on through stool
- If ‘pass’, donation time coordinated with patient drug taper
• Fresh homogenate instilled into patient within a few hrs of preparation
  • Rectal enema
  • Colonoscopy
  • Nasoduodenal tube
  • “Poop pills”

• Results in cure of the patient in >90% of cases
• Rapid resolution of CDI
• Only rare recurrence of disease
Pros and cons of fecal transplants

• Pros:
  • They work! ~90% of patients are cured of CDI
    • Van Nood et al., NEJM 2013
  • They’re comparatively cheap

• Cons:
  • Somewhat primitive
  • Undefined; will vary donor to donor
    • How do you know who’s healthy?
  • Despite screening, still much potential for spread of pathogens
  • They’re gross – lots of psychological stigma
Microbial Ecosystem Therapeutics

- Isolation of a 33-strain, 25 species microbial ecosystem derived from a single, very healthy donor
  - Tested for ecosystem stability *in vitro* (Robogut)
- Copies the fecal transplant approach to treatment of gut disease
  - But is safer, more acceptable, more stable and completely defined

“RePOOPulate”
“RePOOPulate”
for treatment of *C. difficile* infection

- *Acidaminococcus intestinalis*
- *Bacteroides ovatus*
- *Bifidobacterium adolescentis* (x2)
- *Bifidobacterium longum* (x2)
- *Collinsella aerofaciens*
- *Dorea longicatena* (x2)
- *Escherichia coli*
- *Eubacterium eligens*
- *Eubacterium limosum*
- *Eubacterium rectale* (x4)
- *Eubacterium ventriosum*
- *Faecalibacterium prausnitzii*
- *Lactobacillus casei*
- *Lactobacillus paracasei*
- *Parabacteroides distasonis*
- *Raoultella* sp.
- *Roseburia faecalis*
- *Roseburia intestinalis*
- *Ruminococcus torques* (x2)
- *Streptococcus mitis*
- Likely novel species (x5)
- Likely novel genus & species (x1)

Not just the usual probiotic subjects!
RePOOPulate proof-of-principle trial

- 2 elderly ladies with severe, recurrent *C. diff* infections were treated (April and June 2011)
- RePOOPulate made fresh at Guelph, driven to KGH, and administered via colonoscopy
  - 1 dose, 100mLs
- Both patients recovered within 2 days and have remained *C. diff*-free ever since (despite numerous subsequent antibiotic exposures)
Drugs from bugs

• RePOOPulate is the prototype for a new class of drug
  – Currently ‘MET-1+’ is in development for a clinical trial (oral delivery, as a capsule of freeze-dried bacteria)

• We are also developing a series of MET products to treat different diseases
  – Different healthy host sources
  – Different host lifestyles for different donors?
Microbes work better in teams

- Probiotic strains vs. probiotic ecosystems

Probiotic strains, no gut colonization

Microbial synergy, gut colonization
Coming soon, to a health practice near you...

- Gut microbial ecosystem check-ups, to include:
  - Measurement of the metabolic output of patient gut microbiome
  - Recommendations about particular foods that may be important to individual patients’ gut microbes for promoting optimal health
  - Smarter approaches to antibiotic administration
  - Monitoring of antibiotic/enteric infection-induced damage to the microbiome
  - Where there is damage, ecosystem restoration therapies
    - E.g. MET-type approaches
To help maintain health, remember the gut microbiota 3 R’s:

- **Recognize** that we are custodians of a microbial ‘organ’

- **Respect** what the microbes within this organ do for us

- **Reinforce** their beneficial activities
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I found the problem, Mr. Smith. Instead of probiotics, you have been taking amateur biotics.