Mining the gut microbiota for solutions to infectious disease and antibiotic resistance

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This Presentation

• Scale of the problem – Infectious Disease & Antimicrobial Resistance

• Key study on sepsis in India

• Understanding mechanisms
  * C. difficile
  * L. monocytogenes
  * S. Typhimurium

• Future Perspectives

The Human Superorganism

• Metabolism > Liver
• Energy extraction – fat deposition
• Immune regulation
• Barrier to infection

Work from APC Microbiome Ireland & Other Published Sources
• Mortality due to respiratory tract infection and diarrheal disease remains significant
Scale of the Problem – Infectious Disease & Sepsis

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- Foodborne/diarrheal disease a particular concern but potentially a target for interventions.
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Disability-adjusted Life years (DALYs)


Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study

Kristina E Rudd, Sarah Charlotte Johnson, Kareha M Agha, Kately Chinese Shockett, Derrick Tsoi, Daniel Rhodes Kidman, Danny V Colomb, Kevin S Ikuta, Minarjan Bisson, Simon Finch, Carolin Fleischmann-Struck, Flavia R Machado, Konrad K Reinhart, Kathryn Rowan, Christopher W Seymour, R Scott Watson, T Eoin West, Fatima Malindo, Simon Haya, Rafael Lozano, Alan D Lopez, Derek C Angus, Christopher J L Murray, Mohsen Naahhov

Lancet 2020; 395: 200–11

- First global analysis of sepsis

- Found that the global burden of sepsis in 2017 was 48.9 million cases and 11 million deaths

- Twice that of previous ‘estimates’

**Scale of the Problem – Infectious Disease & Sepsis**

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Scale of the Problem – Antibiotic Resistance

Global Impact of Antimicrobial Resistance on Human Health

700,000
AMR related deaths per year globally

58,000
newborns die
58,000 newborns in India die per year as a result of drug-resistant infections

490,000
new cases of multi-drug resistant TB per year

874,541
Total disability adjusted life years due to AMR in the EU per year

30%
Only 30% of developing countries to have an National Action Plan (NAP) on AMR

$100 trillion loss
AMR is predicted to contribute to a 100.2 trillion USD loss to world GDP by 2050

7/8
travellers return home with drug-resistant bacteria

87.5% of travellers to India returned to western Europe carrying drug-resistant bacteria in their gut
Antibiotic resistance genes (incl carbapenem resistance) reside in the gut

Significant need for microbiota-based therapies to reduce:

- Incidence of infection (incl. foodborne)
- Rates of sepsis (immune modulation?)
- Carriage of Anti-microbial resistance
Evidence: Synbiotic Reduces Sepsis

A randomized synbiotic trial to prevent sepsis among infants in rural India

Pinaki Panigrahi1,2, Sailajanandan Parida3, Nima C. Nanda3, Radhanath Satpathy4, Lingaraj Pradhan6, Dinesh S. Chandel7, Lorena Baccaglini1, Arjit Mohapatra5, Subhranshu S. Mohapatra5, Pravas R. Misra3, Rama Chaudhry8, Hegang H. Chen9, Judith A. Johnson10, J. Glenn Morris Jr.10, Nigel Paneth11 & Ira H. Gewolb12

• Synbiotic = *Lb. plantarum* + fructooligosaccharide
• Reduced risk of sepsis by 40%
• Reduced respiratory tract infection
• Prevention better than cure
• Would reduce need for antibiotic
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Colonization Resistance – *Clostridioides difficile*

- 81-96% cure rates
- Better than antibiotic standard of care treatments
- Effective in critically ill patients
**Clostridioides difficile**

Normal microflora vs. Antibiotic-perturbed intestinal microflora.

- Normal microflora:
  - Primary bile salts → Secondary bile salts
  - C. scindens
  - Germination of C. difficile (spore) → Vegetative growth of C. difficile (vegetative)
  - No toxin production

- Antibiotic-perturbed microflora:
  - Primary bile salts → Secondary bile salts
  - Inhibition of vegetative growth
  - Germination of C. difficile (spore) → Vegetative growth of C. difficile (vegetative)
  - Toxin production

Treatment with FMT:

*Buffie et al., Nature. 2015; Brown et al. BMC Gastro 2018*
Bacteriocin (Thuricin) inhibits *C. difficile*

**Thuricin CD**

Thuricin CD; a two component bacteriocin

30,000 sporeformers

Overlaid with *Clostridium difficile*

Rea *et al.*, 2010 *PNAS*; Rea *et al.* 2011 *PNAS*; Rea *et al.* 2014 *Microbiology*
Thuricin specifically targets *C. difficile* & is active *in vivo*
Probiotic mechanisms & \textit{Listeria monocytogenes}

Infectious Cycle

Colin Hill

Corr et al., PNAS 2007

Log CFU/g

Liver

Placebo  Lb. casei NCD01205  Lb. acidophilus NCD01748  Lb. salivarius UCC118  Lc. lactis NZ9000  B. longum JCW7050  B. infantis CCG36569  B. breve UCC2003

Corry et al., PNAS 2007

Colin Hill
**Probiotic mechanisms & Listeria monocytogenes**

*Lb. salivarius*

UCC118 produces a bacteriocin active against *Listeria*

Claesson, M et al. PNAS. 2006. 103:6718-23.

Creation of UCC118 Bac- mutant

![Graph showing CFU/Liver as a % of control for L. monocytogenes EGD-e with UCC118 and Bac- mutant comparisons.]

**Sinead Corr**, Christian Riedel, Yin Li, Paul O’Toole
Probiotic mechanisms & *Listeria monocytogenes*

Sinead Corr, Christian Riedel, Yin Li, Paul O'Toole

Immune strain no longer susceptible to UCC118 *in vivo*

Corr et al., PNAS 2007
Specific Commensals & *Listeria monocytogenes*  

T0 \hspace{1cm} STOP \hspace{1cm} T1 \hspace{1cm} T2 \hspace{1cm} T3 \hspace{1cm} T4

Microbiota Perturbation \hspace{1cm} (Antibiotics or Diet) \hspace{1cm} Analyze for Return of Colonization Resistance

Susceptible to Infection \hspace{1cm} Resistant to Infection \hspace{1cm} Resistant to Infection

A 4-strain consortium of *Clostridium* spp. protected against *Listeria* infection.

Becattini et al., 2017 *J Exp med*
Role of diet in colonization resistance

Oral *L. monocytogenes* Infection

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chow vs LF</th>
<th>Chow vs HF</th>
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<tbody>
<tr>
<td>TNF alpha</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FamP5</td>
<td>NS</td>
<td>***</td>
</tr>
<tr>
<td>IL-1 beta</td>
<td>NS</td>
<td>***</td>
</tr>
<tr>
<td>IFN gamma</td>
<td>NS</td>
<td>***</td>
</tr>
<tr>
<td>IFN-gamma</td>
<td>NS</td>
<td>***</td>
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<tr>
<td>IL-10</td>
<td>NS</td>
<td>***</td>
</tr>
<tr>
<td>Ccl2</td>
<td>NS</td>
<td>***</td>
</tr>
<tr>
<td>Il-23</td>
<td>NS</td>
<td>***</td>
</tr>
<tr>
<td>Il-6</td>
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<td>***</td>
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<tr>
<td>Inos</td>
<td>NS</td>
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<tr>
<td>Mx2</td>
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<tr>
<td>Il-27a</td>
<td>NS</td>
<td>***</td>
</tr>
<tr>
<td>Rcg-gamma</td>
<td>NS</td>
<td>***</td>
</tr>
</tbody>
</table>

Host Immune Response

Low Fat Chow High Fat

Day 0

Immune modulation caused by dietary changes

Day 13

Effects caused by diet vs caused by *Listeria*

Day 16

Las Heras et al., 2019 *Microbiome*
A commensal enhances colonization resistance

Oral *L. monocytogenes* Infection

Las Heras et al., 2019 *Microbiome*
Role of diet in colonization resistance to *Salmonella*

Wotzka et al. 2019 Nat Microbiol

- High Fat Diet promotes *Salmonella* survival in the gut
- Linked to elevated bile acid production
- Commensal *E. coli* (probiotic) protected against this effect
Understanding Colonization Resistance & Rational Probiotic Selection

Ducarmon et al., 2018. Micro. & Mol. Biol. Rev
Conclusions & Future Directions

• Probiotics a very real prospect for preventing infectious disease

• Probiotics a prospect for reducing carriage of resistant bacteria

• Understanding mechanisms important to optimise selection

• Increased appreciation of mechanisms is necessary

• Understand shared mechanisms – resistance to multiple pathogens

• Role of microbiota in sepsis / immune regulation?
Vanessa Ias Heras
Silvia Melgar
Colin Hill

Paul Ross, Mary Rea
Sinead Corr, Paul O’Toole, Christian Riedel, Pat Casey

Thank-you!