The Potential For Microbiome Modification In Critical Illness

Deborah Cook
Objectives

To review

• The microbiome & concepts about its modification during critical illness

• Interventions
  – Predisposition to VAP and Clostridium difficile
  – Primary prevention for VAP
  – Primary & secondary prevention for Clostridium difficile infection
What Is the Microbiome?

- Ecological community of commensal, symbiotic and pathogenic microorganisms ..... in us or on us
- 10x more microbial than human cells
- **Microbiota** -- the microorganisms
- **Microbiome** -- their collective genomes
Living
With our Microbiome

- Microbiome reflects 1-3% of body weight
- 1990’s research on the gut microbiome has flourished leading to the question:
  - Is the mammalian immune system, which seems to be designed to control microorganisms, actually controlled by microorganisms?
- 2008 NIH launch : Human Microbiome Project
Figure. Microbial Biogeography and Community Stability in the Human Body

Microbial ecological zones

FRONT

BACK

Stability landscape of the human microbial ecosystem

Stable state 1

Stable state 2

Environmental change

Skin
- Moist
- Sebaceous
- Dry
- Oral
- Small intestine
- Large intestine

Landscape
- Unstable
- Stable
The Human Microbiome

We can use a genetic “barcode” unique to each species of bacteria to define a community of bacteria.

Each type of bacteria has a distinct barcode or DNA signature.
The Human Microbiome

The barcodes let us measure the diversity of bacteria present.

Classify them into groups

Make plots of the composition to compare
Influences on The Microbiome

• Microbiome diversity is correlated with better health, but may be decreased today by
  – Cesearean sections
  – Formulae feeding
  – Hygiene
  – Processed food
  – Indoor living
  – Antibiotics (animal, human)
  – Achlorhydia

• The microbiome is modified critical illness

• Interventions to modify the microbiome may help to restore health & attenuate disease
Extreme Dysbiosis of the Microbiome in Critical Illness

Daniel McDonald, a Gail Ackermann, a Ludmila Khailova, b Christine Baird, b Daren Heyland, c Rosemary Kozar, d Margot Lemieux, c Karrie Derenski, e Judy King, f Christine Vis-Kampen, f Rob Knight, a Paul E. Wischmeyer b

• **Objective:** to characterize microbiomes by fecal, oral and skin sampling from 115 critically ill patients within 48h of ICU admission & day 10 or ICU discharge

• **Premise:** microbiome data may provide first steps toward diagnostic and therapeutic interventions using microbiome signatures

• **Setting:** 4 mixed ICUs in Canada & US
• **Methods:** processing according to Earth Microbiome Project protocols

• **Results:**
  – Compositions were uncharacteristic of expected community type
  – Critical illness rapidly leads to significant dysbiosis
  – Many taxons of health-promoting bacteria are significantly depleted
Top=admission
Bottom=DC communities

Samples at DC
Include gut bugs, bugs around decomposing bodies, dust samples
Objective: to conduct a series of experiments to evaluate whether the gut microbiota are implicated in the development of ARDS & sepsis

Methods:
- Murine model of sepsis
- Human model of ARDS
- Sequencing of bacterial 16S ribosomal RNA-encoding genes
Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome

Robert P. Dickson¹*, Benjamin H. Singer¹, Michael W. Newstead¹, Nicole R. Falkowski¹, John R. Erb-Downward¹, Theodore J. Standiford¹† and Gary B. Huffnagle¹,²†

**Results:**

- Gut-associated bacteria (particularly *Bacteroides*), undetectable via conventional culturing, enriched the lung microbiome in a murine model of sepsis and human ARDS
- Alveolar TNF-alpha (ARDS mediator of alveolar inflammation) correlated with altered lung microbiota
- Ecological analysis showed persistence for days
Oral Microbiome

- 300+ types of bacteria in the oropharynx
- Dental plaque builds over time & is a reservoir for oral pathogens
- Micro-aspiration of bacteria is common
- Bio-film on ETT also facilitates direct entry of bacteria into the lungs
What are Probiotics?

Commercially available microorganisms which, when ingested as individual strains or in combinations, offer potential health benefits to the host

World Health Organization
Proposed Mechanisms of Benefit

- Re-inoculation of indigenous microflora
- Colonization resistance
- Increase tight junctions & reduce bacterial translocation
- Inhibit pathogen adhesion & invasion
- Re-establish microbiome diversity
- Improve gut barrier function (mucous production)
- Toll-like receptor-mediated up-regulated immunity
- In a trauma RCT (N=52, Tan et al Crit Care 2011)
  - faster increase in T helper 1 cytokines IL-12 p70
  - improved cellular immunity & macrophage function
Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis

William Manzanares¹, Margot Lemieux², Pascal L. Langlois³ and Paul E. Wischmeyer⁴∗

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
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<tbody>
<tr>
<td>Kozampassi 2006</td>
<td>19</td>
<td>35</td>
<td>0.68 [0.48, 0.97]</td>
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</tr>
<tr>
<td>Klarin 2008</td>
<td>1</td>
<td>23</td>
<td>0.30 [0.03, 2.70]</td>
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<tr>
<td>Forestier 2008</td>
<td>19</td>
<td>102</td>
<td>0.94 [0.54, 1.64]</td>
<td>2008</td>
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<tr>
<td>Knight 2009</td>
<td>12</td>
<td>130</td>
<td>0.70 [0.35, 1.41]</td>
<td>2009</td>
</tr>
<tr>
<td>Morrow 2010</td>
<td>13</td>
<td>73</td>
<td>0.46 [0.26, 0.82]</td>
<td>2010</td>
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<tr>
<td>Barraud 2010</td>
<td>23</td>
<td>87</td>
<td>1.41 [0.79, 2.51]</td>
<td>2010</td>
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<tr>
<td>Tan 2011</td>
<td>7</td>
<td>26</td>
<td>0.54 [0.26, 1.13]</td>
<td>2011</td>
</tr>
<tr>
<td>Rongrungruang 2015</td>
<td>18</td>
<td>75</td>
<td>0.82 [0.48, 1.40]</td>
<td>2015</td>
</tr>
<tr>
<td>Zeng 2016</td>
<td>43</td>
<td>118</td>
<td>0.72 [0.54, 0.97]</td>
<td>2016</td>
</tr>
</tbody>
</table>

Total (95% CI) 669 657 100.0% 0.74 [0.61, 0.90]

Total events 155 202

Heterogeneity: Tau² = 0.02; Chi² = 9.86, df = 8 (P = 0.27); I² = 19%

Test for overall effect: Z = 3.04 (P = 0.002)

Fig. 2 Effects of probiotics therapy on the incidence of ventilator-associated pneumonia (n = 9). CI confidence interval, M-H Mantel-Haenszel test
Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial

Juan Zeng¹, Chun-Ting Wang¹*, Fu-Shen Zhang², Feng Qi², Shi-Fu Wang³, Shuang Ma³, Tie-Jun Wu⁴,

- **Design:** Open label RCT in 235 adults
- **Patients:** Expected to receive MV >48h
- **Bacillus subtilis + Enterococcus faecalis** combination 0.5g tid for 14 days

- Less VAP: 36.4 vs 50.4%, *p*=0.031
- Later Time to VAP: 10.4 vs 7.5 days, *p*=0.022
- Fewer gastric PPMO: 24.0 vs 44.0%, *p*=0.004
Strategy with best cost-benefit ratio:
+ Suction ETT
+ IHI Bundle with oral care
+ Probiotics

2014 Compendium of Strategies to Prevent Healthcare Associated Infections in Acute Care Hospitals

Please refer to VAP Prevention Guidelines for more preventive strategies
PROSPECT

PRObiotics to prevent Severe Pneumonia and Endotracheal Colonization Trial

N=2650 mechanically ventilated patients
Probiotics for the Prevention of *Clostridium difficile*-Associated Diarrhea

A Systematic Review and Meta-analysis

Bradley C. Johnston, PhD; Stephanie S.Y. Ma, MD; Joshua Z. Goldenberg, BSc; Kristian Thorlund, PhD; Per O. Vandvik, MD, PhD; Mark Loeb, MD; and Gordon H. Guyatt, MD

- **Population:** children & adults receiving antibiotics
- **Intervention:** any probiotic
- **Control:** placebo
- **Outcome:** CDAD
- **Type:** randomized trials

20 trials enrolling 3,818 patients
Probiotics for the Prevention of *Clostridium difficile*–Associated Diarrhea

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- **Pooled relative risk 0.34 (0.24-0.49), I²=0%**
- Robust to worst assumptions about loss to follow-up
- Quality of evidence: moderate
- Subgroups show consistent benefit
  - Children and adults
  - Probiotic dose
  - Species (single or multiple)
  - Species (L acidophilus+L casei, L rhamnosis, S boulardii)
  - Risk of bias
Canadian Research

• 2 low-tech, low-cost, widely available interventions influence the microbiome of the respiratory tract and gut differentially
  – probiotics
  – acid suppression

• Understanding their impact on nosocomial infections is underway
# Probiotics & Stress Ulcer Prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>PROSPECT</th>
<th>REVISE</th>
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<tbody>
<tr>
<td><strong>Control</strong></td>
<td>Placebo</td>
<td>PPI</td>
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<tr>
<td><strong>Intervention</strong></td>
<td>Probiotics</td>
<td>Placebo</td>
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<td><strong>Primary Outcome</strong></td>
<td>VAP</td>
<td>Clin imp upper GI bleeding</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td>Infections</td>
<td>VAP and C diff</td>
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<td></td>
<td>including C diff</td>
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</table>
• **Design:** blinded non-inferiority RCT

• **Population:** 219 patients ≥18 years old with recurrent *Clostridium difficile* (ELISA or PCR with 3 unformed stools in 24 h) in 6 Canadian centers (secondary prevention)

• **Frozen** fecal microbiota transplantation

• **Thawed** fecal microbiota transplantation
Table 3. Primary Efficacy Outcome in the Modified Intention-to-Treat and Per-Protocol Populations According to Subgroup at 13 Weeks After Last Fecal Microbiota Transplantation

<table>
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<th>mITT</th>
<th>Per-Protocol</th>
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<tbody>
<tr>
<td></td>
<td>Proportion With Clinical Resolution, No./Total (%)</td>
<td>Proportion With Clinical Resolution, No./Total (%)</td>
</tr>
<tr>
<td></td>
<td>Frozen</td>
<td>Fresh</td>
</tr>
<tr>
<td>Overall Population</td>
<td>81/108 (75.0)</td>
<td>78/111 (70.3)</td>
</tr>
</tbody>
</table>

CONCLUSIONS AND RELEVANCE  Among adults with recurrent or refractory CDI, the use of frozen compared with fresh FMT did not result in worse proportion of clinical resolution of diarrhea. Given the potential advantages of providing frozen FMT, its use is a reasonable option in this setting.
Duodenal Infusion of Donor Feces for Recurrent 
Clostridium difficile

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D.,
Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D.,
Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D.,
Marcel G.W. Dijkstra, Ph.D., and Josbert J. Keller, M.D., Ph.D.

• **Design:** open label 3-arm RCT
• **Population:** 43 patients ≥65 years with recurrent *Clostridium difficile* infection following ≥1 antibiotic course (secondary prevention)
• 500mg vancomycin qid PO x 4 days, *then bowel lavage + NG infusion of donor feces*
• 500mg vancomycin qid PO x 14 days
• 500mg vancomycin qid PO x 14 days, *bowel lavage*
After donor feces, increased fecal bacterial diversity
Infusion of donor feces was significantly more effective to cure recurrent *C difficile* (trial stopped early)
Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*  

NEJM 2011

- **Design:** blinded non-inferiority RCT
- **Population:** 629 patients ≥16 years of age with *Clostridium difficile* infection in 52 US + 15 Canadian centers (up to 4 doses of metronidazole or vancomycin allowed) (secondary prevention)
- **Fidaxomicin** 200mg bid PO x 10 days
- **Vancomycin** 125mg qid PO x 10 days
In conclusion, fidaxomicin and vancomycin have similar effectiveness with respect to the clinical resolution of acute diarrheal disease due to *C. difficile* infection, but more sustained or durable resolution of disease (i.e., improved global cure) is achieved with fidaxomicin — a finding that may be attributable to lesser impairment of the intestinal microbiome during treatment of the infection.
Conclusions

• The microbiome is modified in critical illness, but our understanding is still emerging

• Current interventions may influence the microbiome of the respiratory tract & gastrointestinal tract

• Understanding whether microbiome modification can decrease the risk of nosocomial infections is a clinical & research priority
Thank you!