A METAGENOMIC APPROACH TO DIAGNOSIS, INDUCTION AND MAINTENANCE OF DEEP REMISSION FOLLOWING EXCLUSIVE ENTERAL NUTRITION IN PEDIATRIC CROHN’S DISEASE: MAREEN-STUDY
NASPghan/CCFA YOUNG INVESTIGATOR DEVELOPMENT AWARD 2013-2015
JOHAN VAN LIMBERGEN MD FRCPCH PhD

DISCLOSURE & FUNDING
TRAVEL GRANTS / SPEAKER FEES / EDUCATIONAL + RESEARCH GRANT SUPPORT:
ABBvie, APTALIS, JANSSEn, NEStLE, P&G, MERCK, SCHering-PLOUGH
Group similar 16S rRNA sequences into OTUs
Identify OTUs via database
OTU abundance and species interactions

Structure, function and diversity of the healthy human microbiome

SCIENCE VOL. 334 2 JUNE 2012
The Treatment-Naïve Microbiome in New-Onset Crohn’s Disease

The dysbiosis index does not distinguish children with Crohn’s disease from healthy siblings.
EEN VS NOT EATING…

EXCLUSIVE ENTERAL NUTRITION THERAPY IN PEDIATRIC CROHN’S DISEASE PATIENTS RESULTS IN LONG-TERM AVOIDANCE OF CORTICOSTEROIDS: RESULTS OF A PROPENSITY SCORE-MATCHED COHORT ANALYSIS

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CD Patients (n = 128)

EEN (n = 86)  Corticosteroids (n = 42)

Propensity Analysis: Matched groups

EEN (n = 73)  Corticosteroids (n = 35)

Propensity Score-Matched Group Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Corticosteroids (n=72)</th>
<th>EEN (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.3 ± 3.6</td>
<td>11.5 ± 3.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.2 ± 15.4</td>
<td>158.0 ± 14.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>45.2 ± 12.2</td>
<td>-1.7 ± 6.5</td>
</tr>
<tr>
<td>BMI</td>
<td>18.7 ± 2.4</td>
<td>20.3 ± 3.8</td>
</tr>
<tr>
<td>PDCM</td>
<td>36.4 ± 3.3</td>
<td>36.5 ± 3.8</td>
</tr>
</tbody>
</table>

Number of patients with a change in PANS disease classification

<table>
<thead>
<tr>
<th>Disease Classification</th>
<th>Corticosteroids 2 (n=13)</th>
<th>EEN 2 (n=13)</th>
<th>4 Year 2 (n=13)</th>
<th>4 Year EEN (n=15)</th>
</tr>
</thead>
</table>

Linear Growth

- Corticosteroids
- EEN

Proportions of EEN Patients Requiring Steroids

<table>
<thead>
<tr>
<th>Year</th>
<th>Corticosteroids</th>
<th>EEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>20</td>
<td>20</td>
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<tr>
<td>4</td>
<td>20</td>
<td>20</td>
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<tr>
<td>6</td>
<td>20</td>
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Hospitalization at Follow-up

<table>
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<tr>
<th>Year</th>
<th>Corticosteroids</th>
<th>EEN</th>
</tr>
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Surgical Intervention at Follow-up

<table>
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<tr>
<th>Year</th>
<th>Corticosteroids</th>
<th>EEN</th>
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</table>
MAREEN

Metagenomic approach to CD
Diagnosis
Induction
Remission
Using EEN

NASPghan 2015
UEGW 2015

Original Contributions

The American Journal of GASTROENTEROLOGY

Open

Microbiota of De-Novo Pediatric IBD: Increased Faecalibacterium Praunzitzii and Reduced Bacterial Diversity in Crohn’s But Not in Ulcerative Colitis

EEN BASELINE – 12 WEEKS

Clinical remission induced by exclusive enteral nutrition (EEN) in pediatric Crohn’s disease is associated with community level changes in metabolic functions

NASPghan 2015
UEGW 2015
Figure 1. Alpha diversity plots of patients during treatment.

Figure 2. Beta diversity plot of controls and patients based on unweighted UniFrac.

Figure 3. Average relative abundance of Classes during EEN treatment and in controls. Data was inferred from 16S sequences collected from stool samples processed using QIIME.
Figure 4. Biomutat analysis. Week 6 and 8 samples have a stronger mutual system 3 component. Mutual system 9 has a large contribution from subnetwork 70 and is lacking in subnetwork 34. The differential prevalence of the pathways that make up these subnetworks is corroborated by STAMP functional profiles (Fig S5). Arrow indicates patient that relapsed.

OTU structure: phylogenetic relationships
OTU counts: assemblage structure:
positive and negative OTU co-occurrence across samples
identify OTUs
identify and determine abundance of all OTUs within a sample
learn how OTUs contribute to assemblages
learn how community structure is related to patient covariates

Figure 5. Microbial metabolic functions related to pathways identified in metabolysystem 3. Proportion of sequences from each group (BL-baseline, W6-week 6, W8-week 8, W12-week 12, and Ccontrol) involved in the pathways identified in metabolysystem 3. Plots are from metagenomic data analyzed using HUMANN and plotted using STAMP. P-values are corrected for multiple testing.

IBD samples have a community structure
Healthy samples have a community structure
OTU matrices
OTU structure: phylogenetic relationships
NEW APPROACHES TO EEN / PEN

Partial Enteral Nutrition with a Crohn’s Disease Exclusion Diet Is Effective for Induction of Remission in Children and Young Adults with Crohn’s Disease

Andre Segal-Brochet, RD,* Tamara Pfleger-Gal, RD,* MR Segal, MD,* Iuli Zimyan, MD,* Penny Bews, RD, RD,* and Ann Cerny, RD, MT

Inflamm Bowel Dis • Volume 20, Number 8, August 2014

SUMMARY

- BISCUIT-COHORT: WHOLE METAGENOME + WHOLE GENOME: ONGOING
- MAREEN – INDUCTION
- MAREEN – MAINTENANCE
- NEW FUNDING MADE POSSIBLE THROUGH NASPGHAN/CCFA GRANT