Program

World Congress of Pediatric Gastroenterology, Hepatology and Nutrition
October 5-8, 2016 • Montréal • Canada

Dedicated to the memory of
Dr. Claude Roy

Friday, October 7 - Saturday, October 8, 2016
Council for Pediatric Nutrition Professionals (CPNP)
Nutrition Symposium
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>New treatments or therapies for upper GI motility disorders</td>
<td>7</td>
</tr>
<tr>
<td>Carlo Di Lorenzo, MD</td>
<td></td>
</tr>
<tr>
<td>Nutritional aspects in managing the patient with gastroparesis</td>
<td>21</td>
</tr>
<tr>
<td>Carol Rees Parrish, MS, RD</td>
<td></td>
</tr>
<tr>
<td>Long-term effects of parenteral nutrition: The role of lipid emulsions</td>
<td>31</td>
</tr>
<tr>
<td>Marialena Mouzaki, MD, MSc</td>
<td></td>
</tr>
<tr>
<td>Parenteral nutrition in 2016: To wean or not to wean?</td>
<td>43</td>
</tr>
<tr>
<td>Kelly Tappenden, RD, PhD</td>
<td></td>
</tr>
<tr>
<td>Food in children with functional abdominal disorders</td>
<td>53</td>
</tr>
<tr>
<td>Bruno Chumpitazi, MD, MPH and Kristi L. King, MPH, RDN, CNSC, LD</td>
<td></td>
</tr>
<tr>
<td>Introduction of complementary feeding: Lessons from allergy and celiac disease studies</td>
<td>77</td>
</tr>
<tr>
<td>Ranaan Shamir, MD</td>
<td></td>
</tr>
<tr>
<td>Are we LEAPing into an EATing disaster? Early life nutrition and allergy outcomes</td>
<td>89</td>
</tr>
<tr>
<td>Carina Venter PhD RD</td>
<td></td>
</tr>
</tbody>
</table>
President’s Welcome

I would like to welcome you all to our first Nutrition Symposium as part of a World Congress of Pediatric Gastroenterology, Hepatology and Nutrition. We are very fortunate to have a spectacular line-up of speakers from around the world. If you have been to past Nutrition Symposiums as part of the NASPGHAN annual meeting, you will notice some differences. We have broken out our program into different sessions on a single topic, with both RD and physician speakers on several different topics. We hope this will give you a well-rounded perspective on these topics. We did not include breakout sessions this year, but we hope you enjoy our new Clinical Research session and Stump the Expert panel.

We are also excited to be part of a joint session on Friday with the Association of Pediatric Gastroenterology and Nutrition Nurses (APGNN) and the Psychology Collaborative Group (PCG). We would love to hear feedback from you regarding this year’s event so we can continue to optimize your learning experience in years to come.

We have experienced continued growth in our Council for Pediatric Nutrition Professionals (CPNP) over this past year. I am delighted to share that we have 180 members as part of our council from throughout North America. We will once again have a brief council meeting during the lunch hour on Saturday. I encourage everyone to attend to learn about what we are currently doing and what we have planned next! At the meeting, I will officially hand off the presidency to our president-elect, Amber Smith. It has been an honor to serve as the first president of this council – I can’t wait to see what the future holds!

We hope you enjoy this year’s symposium! Next year’s Nutrition Symposium as part of the NASPGHAN annual meeting will be November 2-5, 2017 in Las Vegas, NV.

Thank you so much for being here!

Sincerely,

Jenny Crouse, MS, RD, CD, CDE
President, Council for Pediatric Nutrition Professionals
Thanks to the following companies for their support of this event and the establishment of the Council of Pediatric Nutrition Professionals

Abbott Nutrition
Dr. Schar
Mead Johnson Nutrition
Nestlé Nutrition
QOL Medical

Support for this year’s symposium has been generously provided by:

Abbott Nutrition
Mead Johnson Nutrition
Friday October 7, 2016

Joint Sessions with the APGNN and the Psychology Collaborative Group (see APGNN Program)

6:00pm  **CPNP Reception**

Saturday October 8, 2016

7:30-8:00  Breakfast

8:00-8:15  **Welcome**
Praveen Goday MBBS, CNSC, Chair NASPGHAN Nutrition Committee

8:15-9:45  **Motility**

8:15  New treatments or therapies for upper GI motility disorders
_Carlo Di Lorenzo, MD, Professor of Pediatrics, The Ohio State University
Nationwide Children’s Hospital_

Learning objectives:
1. Describe novel diagnostic tests for children with suspected motility disorders
2. Discuss pharmacological and non-medical treatment options for children with gastroparesis and pseudo-obstruction

8:45  “Moving forward” with constipation management: An update
_Khalil El-Chammas, MD, MS, Assistant Professor
Pediatric Gastroenterology, Hepatology and Nutrition
Cincinnati Children’s Hospital and Medical Center, University of Cincinnati_

Learning objectives:
1. Briefly review the pathophysiology of constipation
2. Discuss the treatments of constipation

9:15  Nutritional aspects in managing the patient with gastroparesis
_Carol Rees Parrish, MS, RD, Nutrition Support Specialist
University of Virginia Health System, Digestive Health Center_

Learning objectives:
1. Identify patients at risk for gastroparesis
2. Devise nutritional treatment plan for the patient with gastroparesis

9:45-10:00  Break
10:00 – 11:30 Parenteral Nutrition

10:00 Long-term effects of parenteral nutrition: The role of lipid emulsions
Maria Elena Mouzaki, MD, MSc, Hospital for Sick Children
Learning objectives:
1. Describe the key differences between lipid emulsions used in clinical practice
2. Synthesize the literature investigating the systemic effects of chronic exposure to lipid emulsions
3. Evaluate approaches to managing complications that are secondary to prolonged use of lipid emulsions

10:30 Nutritional management of short bowel syndrome
Olivier Goulet, MD, PhD, Professor of Pediatrics, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Necker-Enfants Malades Hospital, Paris, France
Learning objectives:
1. Review the basics of nutritional management of short bowel syndrome
2. Describe parenteral nutrition alterations that can help protect against long term complications of parenteral nutrition in short bowel syndrome
3. Describe management strategies that can be used to wean patients off parenteral nutrition in short bowel syndrome

11:00 Parenteral nutrition in 2016: To wean or not to wean?
Kelly Tappeden, RD, PhD
Human Nutrition Endowed Professor, University of Illinois at Urbana-Champaign
Learning objectives:
1. Describe the diagnostic criteria and treatment goals for patients with short bowel syndrome
2. Outline the importance of driving intestinal rehabilitation in patients with short bowel syndrome
3. Understand the latest therapeutic options available to patients with short bowel syndrome

11:30-12:30pm Clinical Research Session

INFLUENCE OF DIETITIANS IN PREVENTING PARENTERAL NUTRITION PRESCRIPTION ERRORS IN A PAEDIATRIC SETTING. Millie Garg¹, Michael Swab², Declan Gibney², Jennifer Cohen¹,², Nitin Gupta², Chee (Keith) Y Ooi¹,². ¹University of New South Wales, Randwick, New South Wales, Australia, ²Sydney Children’s Hospital, Randwick, New South Wales, Australia

EARLY ADMINISTRATION OF PARENTERAL CHROMIUM ALLOWS FOR INCREASED GIR IN NEONATES
Kristin Capone, Timothy Sentongo, Dana Weinstein, Ellen Newton, Kristen Wroblewski, Hilary Jericho, Stacy Kahn, Ranjana Gokhale, Stefano Guandalini, University of Chicago Medicine Comer Children’s Hospital, Contributing author, Chicago, IL, USA

BREASTFEEDING AMELIORATES DYSBIOSIS OF GUT MICROBIOTA IN INFANTS BORN BY C-SECTION.
Yuichiro Yamashiro¹, Ravinder Nappal¹, Hirokazu Tsuji², Takuya Takahashi², Koji Nomoto³, Kazunari Kawashima³, Satoru Nagata³, ¹Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan, ²Yakult Central Institute, Kunitachi, Tokyo, Japan, ³Gonohashi Obstetrics & Gynecology Hospital, Koto-ku, Tokyo, Japan, ⁴School of Pediatrics Medicine, Tokyo Women’s Medical University, Shinjuku, Tokyo, Japan

VITAMIN D NON-SUFFICIENCY IS COMMON IN CHILDREN WITH CHRONIC INFLAMMATORY BOWEL DISEASE AND CHRONIC LIVER DISEASE IN A TROPICAL COUNTRY.
Way Seah Lee, Way Seah Lee, Yee Yong Siow, Shin Yi Wong, Sik Yong Ong, Hee Wei Foo, Ruey Terng Ng, Yazid Jalaluddin, University Malaya, Kuala Lumpur, Malaysia
COW’S MILK ELIMINATION FOR TREATMENT OF EOSINOPHILIC ESOPHAGITIS: A PROSPECTIVE PEDIATRIC STUDY. Joshua B. Wechsler, Sally Schwartz, Pratibha G. Hotwagner, Melanie M. Makhija, Ronda Shaykin, Katie Amsden, Kristin Johnson, Maureen Sulkowski, Jessica Ross, Barry K. Wershil, Hector Melin-Aldana, Amir F. Kagalwalla, Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern University, Feinberg School of Medicine, John H. Stroger Hospital of Cook County, Chicago, IL, USA

THE EFFECTIVENESS OF THE IDENTIFICATION AND MANAGEMENT OF FEEDING DIFFICULTIES FOR CHILDREN (IMFED) PROTOCOL ON IMPROVING FEEDING DIFFICULTIES IN CHILDREN SEEN AT THE MEDICAL CITY CENTER FOR DEVELOPMENTAL PEDIATRICS FEEDING CLINIC. Christine Grace Pasana, Mary Jean Guno, The Medical City, Pasig, Philippines

12:30 -1:30pm Lunch/Poster Sessions/Business Meeting

1:30-2:45pm **Food in children with functional abdominal disorders**

*Bruno Chumpitazi, MD, MPH*  
Director, Neurogastroenterology and Motility Program, Texas Children’s Hospital  
Assistant Professor of Pediatrics, Baylor College of Medicine

*Kristi L. King, MPH, RDN, CNSC, LD*  
Senior Dietitian, Texas Children’s Hospital  
Clinical Instructor, Baylor College of Medicine

Learning objectives:  
1. Review impact and pathophysiology of foods in children with FAPD  
2. Review dietary interventions in children with FAPD

2:45-3:45pm **Nutrition Measures in the Prevention of Allergy**

2:45 Introduction of complementary feeding: Lessons from allergy and celiac disease studies  
*Ranaan Shamir, MD, Chairman, Institute of Gastroenterology, Nutrition and Liver Diseases Schneider Children's Medical Center. Professor of Pediatrics, Sackler Faculty of Medicine, Tel Aviv University, Israel*

Learning objectives:  
1. Complementary feedings guidelines should be updated based on recent evidence.  
2. For allergy, introduction at 4 months may be advantageous for some food items, while for celiac disease, the age of introduction may not have a sustained long term effect on disease prevalence.

3:15 Are we LEAPing into an EATing disaster? Early life nutrition and allergy outcomes  
*Carina Venter PhD RD, Research Associate/Dietitian*  
*Cincinnati Children’s Hospital Medical Center*

Learning objectives:  
1. Current advice regarding introduction of food allergens and allergy prevention  
2. The nutritional and feeding implications of early introductions of allergens

3:45-4:00pm Break

4:00-5:00pm **Stump the Expert Session**  
Praveen Goday MBBS, CNSC  
Justine Turner, MD, PhD  
Sally Schwartz, RD, CSP, LDN  
Karen Warman, MS, RD
New treatments for upper GI motility disorders

Carlo Di Lorenzo, M.D.
Twitter: @carlodilorenzo1

No disclosures or conflicts of interest related to this presentation

I will discuss off label use of medications and diagnostic devices and I will do my best to inform the learners when that will occur

Disclosures

Find first what the problem is
If you look for what is causing the early satiety, nausea, vomiting....

You may find this

Symptoms of Eosinophilic Esophagitis by age*

*Median and inter-quartile range, n=103

- Feeding disorder
- Nausea and vomiting
- Abdominal pain
- Dysphagia
- Food impaction

Fraction of Pop.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Fraction</th>
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<tr>
<td>Feeding disorder</td>
<td>13 %</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>26 %</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26 %</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>27 %</td>
</tr>
<tr>
<td>Food impaction</td>
<td>7 %</td>
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Age (Years)

*Median and inter-quartile range, n=103
Or you may find duodenal eosinophilia (if you biopsied): Is it relevant?


Montelukast in dyspeptic children with duodenal eosinophilia

A double blind, randomized, placebo-controlled, cross-over study (n=40)


More tests?
Pediatric normal values?


- Depends upon the meal
- Use adult data for a solid meal (2 large eggs, 2 slides of bread, jam, water, 345 KCal):
  Abnormal >10% left in the stomach after 4 hours, >60% after 2 hours
- No pediatric data available, but look for extremes

Improved manometry?
Esophagus:
3 types of achalasia (type 2 do better)

Gastroparesis in Children: The Benefit of Conducting 4-hour Scintigraphic Gastric-Emptying Studies
(JPGN 2013;56: 439–442)

• 71 patients (32 boys, average age 10.8 yr)
• 62% children had abnormal GES; 23% who had normal values at 2 h had abnormal GES at 4 h (p<0.0001)
• Survey: Only 5 of the top 20 pediatric GI centers in the US conducted 4-h GES
• Conclusions: Extending GES to 4 h resulted in a considerable increase in diagnosis of gastroparesis

SmartPill pH.p Capsule

• 26mm x 13mm
• 5+ day battery life
• Senses and records pH, pressure and temperature data from within the GI tract
• Wirelessly transmits data to the SmartPill Data Receiver
Gastric Emptying
5 hr, 25 min

Wireless Motility Capsule Tracing- Gastroparetic Child

Conclusion: In symptomatic pediatric patients, the wireless motility capsule test is highly sensitive compared with scintigraphic gastric emptying studies in detecting gastroparesis, and seems to be more sensitive than ADM in detecting motor abnormalities.

22 patients (>8 y/o): All had WMC, 21 had complete scintigraphic gastric emptying study data and 20 had complete antro-duodenal manometry data

Conclusion: In symptomatic pediatric patients, the wireless motility capsule test is highly sensitive compared with scintigraphic gastric emptying studies in detecting gastroparesis, and seems to be more sensitive than ADM in detecting motor abnormalities.

Newest test

Gastric Emptying Breath Test (DEBT) - P110015
Getting tissue

Laparoscopic Full-Thickness Intestinal Biopsies in Children
Mark V. Mazziotti and Jacob C. Longer
Department of Surgery, Division of Pediatric Surgery, Washington University School of Medicine, St. Louis, Missouri, USA.

ORIGINAL ARTICLE: Clinical Endoscopy
Gastrointest Endosc 2011;73:949-54
Percutaneous endoscopically assisted transenteric full-thickness gastric biopsy: initial experience in humans
Christopher N. Andrews, MD, FACP, EECPC, Paul Munch, MD, Donald H. Sehel, MD, Wayne T. Foster, MD, EECPC, Marla Woehe, MD, Ross E. Broome, MD, FACP, Seth J. Greenspan, MD, Calgary, Alberta, Canada

Myositis and eosinophilic ganglionitis
(Ruuska TH, Gastroenterology 2002; Schäppi MG, Gut 2003)

Treatments
Prokinetics?

Erythromycin

In patients with poor motility:
Use high doses

ORIGINAL ARTICLE: GASTROENTEROLOGY

JPGN 2012;54: 780-784

Effect of Amoxicillin/Clavulanate on Gastrointestinal Motility in Children

Roberto Gomez, Sergio Ferre, Hayat M. Intraluminal infusion of A/C induced MMCs in 14/18 children
Amoxicillin or clavulanic acid?

Ciciora S, et al. JPGN 2015 Apr 2. [Epub ahead of print]

Colorectal Disease 2010 12, 540–548

10 mg BID starting dose

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<thead>
<tr>
<th></th>
<th>Slow transit constipation</th>
<th>Intestinal pseudo-obstruction</th>
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</thead>
<tbody>
<tr>
<td>Number of patients (% of total)</td>
<td>6 (42.85)</td>
<td>7 (57.15)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24–59</td>
<td>22–80</td>
</tr>
<tr>
<td>Gender</td>
<td>Men 3</td>
<td>Women 4</td>
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<td>Improvement with pyridostigmine (% of group)</td>
<td>3/6 (50.00%)</td>
<td>7/7 (100%)</td>
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<td>Surgery (% of group)</td>
<td>5/6 (83.33%)</td>
<td>2/7 (28.57%)</td>
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</table>

Working on sensation and accommodation...
Old but good…

Cyproheptadine

First generation anti-histamine with additional anticholinergic, antiserotonergic, and local anesthetic properties

J Pediatr 2013 (in press)

80 children (mean age 10 y)

Safety and Efficacy of Cyproheptadine for Treating Dyspeptic Symptoms in Children

J Pédiatr. 2013 (in press)

80 children (mean age 10 y)

Fludrocortisone improves nausea in children with orthostatic intolerance (OI)

17 pts with chronic idiopathic nausea, with orthostatic intolerance by abnormal tilt table tests (88%) or gastric dysrhythmias (71%)

Fludrocortisone: 0.1-0.2 mg/day for 4 weeks
Iberogast

Iberogast is comprised of the following 9 ingredients: *Iberis amara*, Angelica, Chamomile, Caraway Fruit, St. Mary's Thistle, Balm Leaves, Peppermint Leaves, Celandine, and Liquorice Root.

Gastrointestinal Symptom score during 8 wk of treatment with STW 5 (Iberogast) or placebo


Iberogast in Functional Dyspepsia

Hypnotherapy for nausea?

In five of these studies the participants were children. Studies report positive results including statistically significant reductions in anticipatory and CINV. Meta-analysis revealed a large effect size of hypnotic treatment when compared with treatment as usual, and the effect was at least as large as that of cognitive–behavioural therapy.

Acupuncture?

Authors' conclusions: P6 acupoint stimulation prevented PONV. There was no reliable evidence for differences in risks of postoperative nausea or vomiting after P6 acupoint stimulation compared to antiemetic drugs.

Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting (PONV). A Cochrane systematic review and meta-analysis.

Objectives—To determine the efficacy and safety of P6 acupoint stimulation in preventing PONV.

Search strategy—We searched CENTRAL, The Cochrane Library, Issue 3, 2008; MEDLINE (January 1966 to September 2008); EMBASE (January 1988 to September 2008); and Web of Science (January 1985 to September 2008). We searched the National Library of Medicine publication list of acupuncture studies, and reference lists of articles.
More invasive treatments

Botulinum Toxin:
100-200 Units divided in 4 quadrants

Endoscopic intrapyloric injection of botulinum toxin A in the treatment of children with gastroparesis: a retrospective, open-label study (O).

Gastrointest Endosc. 2012 Feb;75:302-9
Gastric Electrical Stimulation (GES): The nausea Holy Grail in pediatrics?

Symptom Severity

Improved total score (p<0.0001)

Efficacy of permanent gastric electrical stimulation for the treatment of gastroparesis and functional dyspepsia in children and adolescents

Steven Teich a,*, Hayat M. Mousa b, Jaya Punati b, Carlo Di Lorenzo b

Neuromusculogenesis & Motility

Improvement of quality of life and symptoms after gastric electrical stimulation in children with functional dyspepsia

F. L. Lu, S. Teich, C. Di Lorenzo, M. Shagii, M. Ahmadi, & H. M. Mousa
Nutritional Aspects of Managing the Patient with Gastroparesis (GP)/Motility Disorders

Carol Rees Parrish MS, RD

Nutrition Support Specialist
University of Virginia Health System, Digestive Health Center
Charlottesville, VA
2016 World Congress of Pediatric Gastroenterology, Hepatology & Nutrition
Montreal, Canada

I have no financial relationships with a commercial entity to disclose.

Spectrum of Pediatric Gastroparesis
n = 239 (%)

- Idiopathic 167 (70)
- Drugs 43 (18)
- Postsurgical 30 (12.5)
- Postviral 12 (5)
- Diabetic 9 (4)
- Other endocrine 8 (3.3)
- Rheumatologic 5 (2)
- Metabolic 4 (1.6)
- Miscellaneous 15 (6.3)

- Comorbidities 92 (38.5)
  - Seizure disorder, cerebral palsy, developmental delay, prematurity
  - Psychiatric disorders 68 (28.4)
  - ADHD, depression, anxiety, bipolar disorder, other behavioral problems

Assessment cont.

- Diet History
  - Typical intake
  - Oral feeding difficulties
  - Use of supplements, etc.
  - Prior nutrition interventions?
  - Food Intolerance/allergies?
    - Meats & Milk/milk products
- Dentition
- Review medications (narcotics, etc.)
- Bowel habits—i.e., constipation!

University of Virginia Health System Digestive Health Center

Common Nutritional Concerns

- Vitamin D
  - 25-OH vitamin D
- Iron studies including:
  - Ferritin in non-acute phase setting
- Glucose
  - Check HgbA1C if DM present or suspected
- Folate
- B12
  - Serum B12, methylmalonic acid

University of Virginia Health System Digestive Health Center

B12 Deficiency

- Bacterial proteases inactivate intrinsic factor
  - Causes malabsorption of B12
  - Captured by anaerobic bacteria in lumen
  - Can convert to physiologically inactive form
- Consider checking:
  - Both serum B12 and methylmalonic acid
  - CBC for MCV (megaloblastic anemia)
- AAFP recommends empiric treatment if B12 < 400pg/dL w/ clinical signs/sx

University of Virginia Health System Digestive Health Center
Nutrition Intervention

“Over the past 3 decades, patients have received dietary advice based on physiological principles rather than evidence.”


Evidence to Date (adults)

- Patient diet surveys
- Observational studies
  - Small “n”
  - Heterogeneous groups
    - Asymptomatic, symptomatic, long-standing DM, etc.
    - Fasting vs. non-fasting
    - DM 1 &/or 2, mixed GP etiologies
- Various single food trials (0-580 kcal):
  - Mashed potatoes, oral glucose, mixed meals, 300mL water

Newer Data

- Compared GI symptoms in DM subjects eating foods easily mashed w/ fork into small particle size vs. normal diet
  - n = 56
  - Documented improvements in key symptoms
- Compared solid vs. liquid meals on GP symptoms by calorie & fat controlled diet
  - 4 meals: 260 kcal each; 2 vs. 13g fat
  - n = 12
  - More symptoms to least:
    - High-fat solid > low-fat solid > high-fat liquid > low-fat liquid

Newer Data (survey) cont.

- Identify and characterize foods provoking or alleviating gastroparesis symptoms via survey
  - n = 45
  - Foods provoking symptoms were generally:
    - Fatty, acidic, spicy, and roughage-based
  - Foods shown to be tolerable were generally:
    - Bland, sweet, salty, and starchy


Figure 1. Patterns of GE of liquids and solids in health and in gastroparesis. GES curves for liquids and solids were derived from the published literature. Low-fat solid meal is a 2% fat, 255-kcal meal; high-fat meal is 32% fat, 296-kcal meal.

Camilleri M. Clin Gastroenterol Hepatol. 2016;14(8):1072-80. Used with permission from Camilleri, Michael, M.D.

Oral Diet Suggestions

- \( \downarrow \) volume of meals
- \( \uparrow \) frequency of meals
- \( \downarrow \) high fiber foods & stool bulking agents
- Fat restriction – with/as solid food
- Chew foods well
- Minced foods over solids
  - Transition to pureed, then liquid consistency
- Positioning (upright vs. supine?)
Enteral Access—When?

- Weight loss/ Failure to gain
  - Ages 2-20 yrs: mild: 5%, moderate: 7.5%, severe: 10%
  - < 2 yrs: inadequate weight gain
- Need for gastric decompression
- Repeated hospitalizations for:
  - Hydration / nutrition / medication delivery
  - DKA
  - Overall quality of life

Enteral - Options

- Non-vented
  - Gastric
  - Nasoduodenal vs. nasojejunal
  - Direct Percutaneous endoscopic jejunostomy
  - Surgical or laparoscopic “J”
- Vented
  - Separate G and J ports
  - Jet-PEG (PEG/J)
    - (Jejunal extensions-12 Fr)

Enteral cont.

A Word About PEG/J’s…

- Abdominal placement is important
- Size of PEG and “j-arm”?
- Where are the feeding ports?
- Medication delivery via J arm
  \( \Rightarrow \) EDUCATION is critical
Enteral cont.

• Strict NPO during EN initiation (x 48 hrs+)
  ▫ Nocturnal vs. continuous
  ▫ If DM present:
    ▪ Accuchecks at 1800, 2200, 0200, 0600 for pts on nocturnal EN x 2 nights

• Formula selection
  ▫ Standard products for majority of patients
  ▫ Avoid fiber-containing products initially

Glycemic Control

• Independently may aggravate symptoms of gastroparesis
• Prevents nutritional repletion
  ▪ “Improve glycemic control to maximize nutrient utilization.”
• Attenuates efficacy of erythromycin
  ⇒ Avoid wide glycemc excursions

Refeeding Risk

• Initiation:
  ▫ Start with 50% goal calories
  ▫ Increase daily by 20% as tolerated
• Adequate vitamins/minerals, esp. thiamine
  ▫ Mg++ may need to replace IV over 10-12 hrs
• Replace electrolytes, but do not hold feeding
• Accelerated in patients started on insulin therapy as hyperglycemia resolves (i.e., DKA)
  ▫ May need prolonged replacement
**Diarrhea/Nausea/Vomiting**

- Review medication list
  - Common offenders include:
    - Acetaminophen elixir, guaifenesin syrup, neutraphos
    - Discontinue standing orders for laxatives, etc.
- Rule out infectious causes
  - C. Difficile
- Adequate anti-emetics/prokinetic agents
  - “PRN” vs. scheduled dosing
  - Route of delivery

**Small bowel bacterial overgrowth**

- Diet (see resource slide)
  - Low fiber
  - Low sugar/s
    - Sugars/fructose/sugar alcohols (sorbitol, etc.)
    - Fruit/ juices
    - High fructose corn syrup (HFCS)/ Honey
- Enteral feeding
  - Avoid fructo-oligosaccharides (FOS)/ fiber

**D-lactic Acidosis**

- (Type of bacterial overgrowth)
- At risk pts:
  - Short bowel syndrome with colon segment
  - Gastric bypass surgery for obesity
    - Diminished colonic motility can contribute
- Symptoms: altered mental status, slurred speech, ataxia, metabolic acidosis (can resemble alcohol intoxication)
- Check D-lactate (not L-lactate)
  - D-lactic acid is > 3mmol/L
D-lactic Acidosis cont.

- Malabsorbed carbohydrate is fermented by d-lactate producing bacteria
- Treatment consists of:
  - Reducing or eliminating oral or enteral carbohydrates
  - Strict NPO short term if needed
  - Correction of metabolic acidosis
  - Sodium bicarbonate enterally or IV
  - Suppression of pathogenic flora/s with antibiotics; sometimes needed long term.
  - Avoid probiotics with D-lactate producing strains if used

SIBO & Rosacea

- One of the most common skin conditions affecting > 16 million in the U.S.
- Resembles acne
- Parodi et al:
  - SIBO found in 52/113 pts w/ rosacea
  - Eradication of SIBO was associated w/ remission of rosacea up to 9 months
- Nationwide cohort study (Egeberg et al):
  - Prevalence of celiac, Crohn’s, UC, H. pylori, SIBO & IBS was higher in pts w/ rosacea compared to controls.

On-Line Resources

- UVAHS GI Nutrition Webpage:
  - www.GInutrition.virginia.edu
- Find links to:
  - Nutrition Articles in Practical Gastroenterology
  - Patient education materials including:
    - Gastroparesis
    - Short & long versions, renal, & diabetes
    - New diet for SIBO
    - Short bowel
    - Low FODMAP
References

**General Gastroparesis**
- Entire issue is dedicated to current understanding & management of gastroparesis:

References cont.

**Gastroparesis & Nutrition**
D-Lactic Acidosis


SIBO & Gastroparesis


SIBO & Rosacea

LONG-TERM EFFECTS OF PARENTERAL NUTRITION: THE ROLE OF LIPID EMULSIONS

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Hospital for Sick Children
University of Toronto

Disclosures

• No financial relationships with a commercial entity to disclose

Learning objectives

1. Describe the mechanisms via which lipid emulsions contribute to liver disease

1. Appraise liver disease outcomes with the use of new generation lipid emulsions

1. Recognize the extrahepatic manifestations of prolonged exposure to lipid emulsions
Lipid emulsions (LE)

<table>
<thead>
<tr>
<th>Generation</th>
<th>Medium</th>
<th>Lipid Phase</th>
<th>Lipid Solvent</th>
<th>Emulsifier</th>
<th>Trace Elements</th>
<th>Antioxidants</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Serum</td>
<td>30% Oil</td>
<td>TPGS 10%</td>
<td>3% Lecithin</td>
<td>0.1% Fe as FeSO4</td>
<td>0.1% Phytosterols</td>
</tr>
<tr>
<td>Second</td>
<td>Serum</td>
<td>30% Oil</td>
<td>TPGS 10%</td>
<td>3% Lecithin</td>
<td>0.1% Fe as FeSO4</td>
<td>0.1% Phytosterols</td>
</tr>
<tr>
<td>Third</td>
<td>Serum</td>
<td>30% Oil</td>
<td>TPGS 10%</td>
<td>3% Lecithin</td>
<td>0.1% Fe as FeSO4</td>
<td>0.1% Phytosterols</td>
</tr>
</tbody>
</table>

### Intestinal Failure Associated Liver Disease (IFALD)

- **Incidence**
  - Overall: 30%
  - ELBW/VLBW on PN: 25%
  - Term infants/children without IF: 35%
  - Pediatric patients with IF: 50%

- **Histologically**
  - Cholestasis
  - Steatosis
  - Inflammation
  - Fibrosis

#### Incidence

- Setting: Incidence
  - Overall: 30%
  - ELBW/VLBW on PN: 25%
  - Term infants/children without IF: 35%
  - Pediatric patients with IF: 50%

- **Antioxidant potential**
  - Phytosterols

#### Pathogenesis: lipid emulsion contribution

- Antioxidant potential
- Phytosterols

50% of infants develop cirrhosis and require liver transplantation to survive.
Phytosterols

- **campesterol**
- **stigmasterol**
- **β-sitosterol**

**LXR and FXR antagonism:**
- $\downarrow$ Abcg5/8 expression
- $\downarrow$ Abcb11 (BSEP), Abcc2 (MRP2) expression

Liver injury severity correlates with stigmasterol concentration in serum and liver

El Kasmi et al. *Sci Transl Med* 2013

IFALD pathogenesis

Phytosterols in children with on PN

- Premature infants (bwt: <1,249 g) randomized to 5 lipid emulsions
- Day 7 and 14 plasma PS levels higher with 100% Soybean oil
- Minimal cholestasis

- 96 VLBW infants randomized to SMOFlipid® vs. Intralipid®
- Cholestasis only in 4% in each group

Levels checked on day 6 & 14

Phytosterols in IFALD correlate with histology

Cross-sectional study:
• Subjects on PN (n=36)
• Subjects previously on PN (n=34)
• Healthy controls (n=86)

In another study of pediatric IF patients, n=7 on PN and n=9 off PN:
• Fibrosis correlated with hepatic stigmastened and campesterol levels

Essential Fatty acids

ω-3 fatty acids
- α-Linolenic Acid
- Eicosapentanoic acid (EPA (20:5))
- Docosahexanoic acid (DHA (22:6))

ω-6 fatty acids
- Linoleic Acid
- Arachidonic Acid (20:4)

Desaturases/elongases

COX
PG, LT
Resolvins
Lipoxins

Significant variation in ω3/ω6 content of available LE

PUFA → peroxidation → ROS → oxidative stress
• Cholestasis secondary to poor bile flow
Fatty acid composition in IFALD

- Limited data in children
- RCT SMOF® vs IL® in neonates with IFALD
  - 8 weeks later, SMOF® associated with ↓LA, ALA and ↑EPA, DHA, OA in RBC membranes
  - 4 weeks post trial no differences between groups
- Prospective cohort study in infants with short bowel syndrome
  - Transition from IL® to Omegaven® due to IFALD (DB>34 umol/L)
  - Omegaven® x 2 x 1 month

<table>
<thead>
<tr>
<th>Variable</th>
<th>First value</th>
<th>Last value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA, 20:4 (μmol/L)</td>
<td>50 (23-115)</td>
<td>103 (60-163)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EPA, 20:5 (μmol/L)</td>
<td>5.0 (2.0-10.4)</td>
<td>6.0 (3.0-12.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DHA, 22:6 (μmol/L)</td>
<td>72 (50-108)</td>
<td>78 (60-98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OA, 18:2 (μmol/L)</td>
<td>278 (123-529)</td>
<td>1008 (539-1579)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Diamond et al., J Parenter Enteral Nutr 2016; Lee et al., J Clin Nutr 2016

Markers of lipid peroxidation in children with IFALD

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Design</th>
<th>Dose/Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goulet et al.</td>
<td>Home PN</td>
<td>RCT IL® vs. SMOF®</td>
<td>2 g/kg/d</td>
<td>29 days</td>
</tr>
<tr>
<td>Skouroliakou et al.</td>
<td>&lt;32 GA or &lt;500g</td>
<td>RCT IL® vs. SMOF®</td>
<td>2.3 g/kg/d</td>
<td>21-49 days</td>
</tr>
<tr>
<td>Deshpande et al.</td>
<td>&lt;30 GA</td>
<td>RCT Clinoleic® vs. SMOF®</td>
<td>≤ 0.6 g/kg/d</td>
<td>7 days</td>
</tr>
<tr>
<td>D’Ascenzo et al.</td>
<td>&lt;30 GA RCT</td>
<td>Clinoleic® vs. SMOF®</td>
<td>7 days</td>
<td>∆lipid peroxidation and ↑EPA with SMOF®</td>
</tr>
</tbody>
</table>


Vitamin E

SMOF® associated with higher vitamin E levels and increased antioxidant potential in premature infants

<table>
<thead>
<tr>
<th>Vitamin E</th>
<th>Level</th>
<th>Mean (mg/L)</th>
<th>Statistically significant (P&lt;0.05)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMOF®</td>
<td>0.47</td>
<td>20-30</td>
<td>-</td>
<td>Increased antioxidant potential</td>
</tr>
<tr>
<td>IL®</td>
<td>0.40</td>
<td>20-30</td>
<td>-</td>
<td>No difference</td>
</tr>
</tbody>
</table>

Skouroliakou et al., Eur J Clin Nutr 2010; Deshpande et al., J Pediatr Gastroenterol Nutr 2014
Liver disease outcomes with the use of new generation lipid emulsions

Hepatic outcomes using 3rd generation LE: Combination lipids

- Heterogeneous literature
- Different lipids compared
- Varied duration of lipid exposure
- Varied dosing of lipid used
- Different outcomes

- Key data (e.g. enteral nutrition) often missing

SMOF® may lead to lower total bilirubin in premature infants

- Total bilirubin assessed at ~2 weeks after PN initiation

<table>
<thead>
<tr>
<th>SMOF® vs. Control</th>
<th>Mean Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower total bilirubin</td>
<td>↓ in TB by 2 mg/dL (95% CI: -4.4 to 0.2; p=0.08)</td>
<td></td>
</tr>
</tbody>
</table>
SMOF® can prevent the progression of IFALD in neonates with IF

- RCT
- Infants
- Mean age: 6 months, GA: 34 weeks
- Median duration of PN exposure: 8 weeks

SMOF® vs. IL®

At study exit,
CB > 50 umol/L:
9% vs. 46% of patients

4 weeks post PN,
CB > 50 umol/L:
27% vs. 69% of patients

Goulet et al.
Home PN patients (total n=28)
RCT: SMOF® vs. IL®
29 days; 2 g/kg/d
TB change (mg/dL):
SMOF® ‐ 0.09 vs. IL® +0.13

Muhammed et al.
Home PN patients (total n=17)
Retrospective: SMOF® vs. IL®
6 months; TB change (mg/dL):
SMOF® ‐ 5.9 vs. IL® +4.6

Pichler et al.
Older children (n=74) with TB>50 mg/dL or LE>x2 ULN following 2 weeks on IL®
Retrospective: SMOF® vs. Lipofundin®
29 days (median); 2.2 g/kg/d
Hyperbilirubinemia resolution in 70% of those on PN>27 days

SMOF® associated with lower TB in hospitalized children on prolonged PN

- 35 children on PN – median age 1.3 months
- 20 on SMOF® followed prospectively
- 15 on IL® retrospective cohort
- At 10 weeks of PN exposure conjugated bilirubin (CB):
  5 vs. 50 umol/L (SMOF® vs. IL®)
- At PN discontinuation CB:
  increased by 10% vs. 53% (SMOF® vs. IL®)
- Four patients on SMOF®>16 weeks later: CB=0
Fish oil based lipid emulsions

- Observational data showing decreases in CB with Omegaven®
  - Omegaven® beneficial when used alone or with low dose IL®
  - Results possibly confounded by lowering dose of Omegaven®

- RCT of 1 g/kg/d of Omegaven® vs. IL® in surgical infants < 3 months old, without IFALD
  - n=9 and 7, respectively; similar enteral intakes
  - At week 4: similar DB levels
  - Early study termination

- RCT of 1.5 g/kg/d of Omegaven® vs. IL® in infants < 3 months old, with IFALD
  - n=9 and 7, respectively
  - At 4 months: no difference in IFALD reversal;
  - Rates of CB and ALT rise lower with Omegaven®

- Paucity of high quality data to support the use of fish oil based emulsions

Biochemical improvement with fish oil does not correlate with fibrosis reversal

- 7 patients with IF on Omegaven® x ~ 62% of their lifespan pre combined liver/intestinal transplant
  - 6/7 patients with ultra-short gut
  - Fish oil introduced at 9 months
  - Fish oil exposure 16 months
    - 1.5 g/kg/d

  - Introduction of fish oil associated with:
    - Reduction in TB by 92% (at transplant TB: 0.7 mg/dL)
    - No change in ALT, albumin, PLT
    - Fibrosis stage 3-4 in liver explant

  - Similar results from 2 case series of 8 children with IFALD on Omegaven

IFALD persists after PN cessation

- Median age 7.2 years
- Current PN exposure
- Histology

- More cholestasis (p=0.02 vs. controls)
- More portal inflammation (p=0.02 vs. controls)
- More portal fibrosis (p=0.04 vs. controls)

- More steatosis (50% vs. 45%) & fibrosis (88% vs. 64%)

- 38 patients with IFALD, 22 weaned off PN earlier (~8.8 years)
- Similar steatosis (50% vs. 45%) & fibrosis (88% vs. 64%)

References:
- Seida et al. J Parent Enteral Nutr 2013

Histology

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- More portal fibrosis (p=0.04 vs. controls)

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References:
- Seida et al. J Parent Enteral Nutr 2013
Extrahepatic manifestations of prolonged exposure to lipid emulsions

Extrahepatic manifestations of LE: BONES
- PUFA affect differentiation and activity of bone cells
- In utero, 5:2 transport of AA:DHA to fetus during 3rd trimester

ω-3 fatty acids are beneficial to bone health
- Increase production of IGF-1
- Improved Ca accretion in bone
- Reduced proinflammatory cytokines
- Animal studies: ω-3 important but not all ω-3 are the same
  - AA/EPA positively correlated with PGE2 and negatively correlated with bone formation rate
  - Lower EPA/DHA ratio (<3:1) may be advantageous for bone mineralization
- Practical challenge: RBC LC-PUFA may not correlate with bone LC-PUFA content in children on PN
Impact of different LE on pediatric bone disease

- Data limited and often confounded
- SMOF® vs. IL® (observational data):
  - SMOF associated with lower ALP in multiple regression analysis* in VLBW infants (~25 days of PN)
  - SMOF NOT associated with different ALP in premature infants on short term PN
- Fractures in PN dependent neonates (>4 weeks of PN):

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Type of fx</th>
<th>Recurrent fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish oil</td>
<td>5%</td>
<td>17%</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>12%</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>17% ribs</td>
<td>67% extremities</td>
</tr>
</tbody>
</table>


Extrahepatic manifestations of LE: BPD

- Observational data suggesting lower incidence of BPD with SMOF® vs. IL® in VLBW infants
- Cochrane review on LE impact on preterm infants
  - Pooled effect towards decreased BPD with olive-soybean LE vs soybean LE – not statistically significant (n=261; studies=4)

Extrahepatic manifestations of LE: ROP

- Photoreceptors are rich in DHA
  - DHA → neuroprotectin D1:
    - Inhibits oxidative stress-mediated apoptosis
    - Promotes retinal pigment epithelial cell survival
- Cochrane review on LE impact on preterm infants – 1 study
  - Combination MCT-olive-fish-soy better than soybean LE in preventing ROP stage 1-2 (NNTB=4) – associated with changes in RBC DHA
  - No difference in ROP ≥3

References:
Neurodevelopmental outcomes

- Conflicting data re: impact of DHA supplementation of diets of premature infants on neurodevelopmental outcomes

- Limited data on impact of LE

- Differences in LE provision in infancy (dose, duration, EFAD) have no impact on neurocognitive assessment at 2–5 years of age

- Further research needed to determine the impact of different LE

Overall outcomes

Impact of LE on overall outcome

- Challenging to isolate LE effect – concurrent changes in care
Conclusions

• Phytosterol content, oxidative stress induction and cytokine release are mechanisms via which LE can contribute to IFALD

• Early data suggest that 3rd generation LE may be advantageous in terms of IFALD prevention/treatment

• Further research is needed to clarify the impact of 3rd generation LE on extrahepatic morbidity and overall mortality

Thank you
Parenteral Nutrition and SBS-IF in 2016: To Wean or Not to Wean?

Dr. Kelly Tappenden, Ph.D., R.D.
Human Nutrition Endowed Professor
University of Illinois at Urbana
Editor-in-Chief, Journal of Parenteral and Enteral Nutrition

Disclosures

Board Member/Advisory Panel/Speaker
• ASPEN Rhoads Research Foundation
• FeedM.E./Alliance to Advance Patient Nutrition
• Dannon Nutrition Institute
• Shire Pharmaceuticals
• Abbott Nutrition
• Nutricia Advanced Medical Nutrition

No products or services produced by these companies are relevant to my presentation.

Learning Objectives

By the end of this session, the participant will be able to:
1. Describe the diagnostic criteria and treatment goals for patients with short-bowel syndrome (SBS)-associated intestinal failure (IF).
2. Outline the importance of driving intestinal rehabilitation in patients with SBS-IF.
3. Understand the latest therapeutic options available to patients with SBS-IF.
Intestinal resection is a surgical procedure in which a part of the large or small intestine is removed. Multiple diseases or events may necessitate resection. Extensive resection may cause malabsorption if the length and quality of the remaining small bowel is inadequate.

Intestinal Adaptation After Resection

- Intestinal adaptation involves:
  - ↑ villus height and crypt depth
  - ↑ digestive and absorptive capacity/cell
  - ↑ transit time
  - ↑ mesenteric blood flow
- Factors that affect the extent of the adaptation include:
  - age
  - length of remaining bowel
  - presence of the ileocecal valve
  - comorbid conditions
  - intestinotropic hormone levels
- The success of the adaptive response impacts absorptive capacity.

Insufficient Adaptation May Result in SBS-IF with Longterm Parenteral Nutrition (PN) Dependency

- Patients with SBS-IF are unable to maintain fluid and nutrient balances through a normal diet.
- Patients with SBS-IF may become dependent on intravenous nutrient/fluid supplementation through parenteral nutrition (PN).
- SBS-IF and PN dependency is associated with many complications and reduced patient survival.
**Disease Management: Overview**

- Reduce malabsorption-related symptoms
- Enhance absorption
- Enable oral/enteral nutrition
- Reduce or eliminate PN
- Minimize PN-related complications

**Improved disease management**

---

**Disease Management: Promoting Intestinal Adaptation**

- Intestinal adaptation can be promoted by multiple non-nutrient factors:
  - Growth hormone (GH), epidermal growth factor, insulin-like growth factors, keratinocyte growth factor, cholecystokinin, gastrin, insulin, and neurtensin
  - Prebiotic/probiotic therapy
  - Glucagon-like peptide-2 (GLP-2)/teduglutide

- Nutrition therapy is an effective stimulant of intestinal adaptation and an essential treatment for SBS-IF

---

**Enteral Nutrition (EN) in Children with Short-Bowel Syndrome**

1. EN should be initiated ASAP after bowel resection to promote intestinal adaptation.
2. EN should be administered in a continuous fashion.
3. Breast milk or standard polymeric formula (depending on child’s age) is preferred.
4. Bottle-feeding (small vols) should be started ASAP in neonates to stimulate the suck/swallow reflexes. Solid food can be introduced at 4-6 months (corrected for GA) to stimulate oral motor activity and to avoid feeding aversion behavior.

---
Tube Feeding ↑ Absorption in SBS-IF Patients

- RCT in 15 SBS-IF patients (>3m past surgery)
- Quantified absorption between:
  1. Isocaloric tube feeding (ETF)
  2. Isocaloric oral feeding (OF)
  3. Oral feeding + 100kcal/d tube (OCEF)
- ETF and OCEF ↑ net absorption of lipids, proteins, and energy compared with OF

ETF and OCEF ↑ net absorption of lipids, proteins, and energy compared with OF

Energy absorption increased by functional colon and high carbohydrate diet

Joly F et al., Gastroenterology 2009;136(3):824-831
Nordgaard et al., Lancet 1994;343:373-376
Colon ‘important in the digestion of carbohydrates and hence in the salvage of calories in patients with SBS…”


Butyrate-supplemented PN increases ileal villous length

Bartholome et al., JPEN 2004;28:210-222.

A clinically feasible approach to butyrate delivery

- Butyrate supplemented PN not currently available
- SCFA are produced in vivo by bacterial fermentation of malabsorbed carbohydrates
- Short-chain fructooligosaccharides (scFOS), a rapidly fermented prebiotic, may be a clinically efficacious means for delivering butyrate
- Synbiotic approach necessary?
Experimental design

- jugular catheterization
- nasogastric tube placement
- 80% jejunoileal resection

n = 96
24h, 3d or 7d

Control
Prebiotic
Probiotic
Symbiotic

20% EN/80% PN
10 g/kg BW FOS
1 x 10^6 CFU LGG
FOS + LGG

Treatment

Ileal villus height ↑ by prebiotic treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>340 ± 28</td>
<td>361 ± 23</td>
<td>375 ± 28</td>
</tr>
<tr>
<td>Prebiotic</td>
<td>405 ± 28</td>
<td>431 ± 23</td>
<td>474 ± 28</td>
</tr>
<tr>
<td>Probiotic</td>
<td>361 ± 27</td>
<td>370 ± 23</td>
<td>408 ± 28</td>
</tr>
<tr>
<td>Symbiotic</td>
<td>371 ± 31</td>
<td>430 ± 26</td>
<td>487 ± 30</td>
</tr>
</tbody>
</table>

Data presented in µm

*Con, Pre, Pro, Syn > Con*

Jejunal amino acid/peptide transport ↑ by prebiotics at 7d

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ΔµA/cm² (10mM glutamine)</th>
<th>ΔµA/cm² (10mM GlySar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Pre</td>
<td>b</td>
<td>ab</td>
</tr>
<tr>
<td>Pro</td>
<td>b</td>
<td>a</td>
</tr>
<tr>
<td>Syn</td>
<td>b</td>
<td>ab</td>
</tr>
</tbody>
</table>

p<0.001
p=0.03
p=0.03
What about humans with intestinal failure?

Intact Gastrointestinal Tract  Short-Bowel Syndrome

Role of GLP-2 in Intestinal Adaptation:
- Peptide hormone produced in ileum and proximal colon
  - Induces local release of growth factors from enteric cells, subepithelial myofibroblasts, and enteric neurons
  - Evidence indicates GLP-2 plays a role in intestinal adaptation:
    - Increased levels after resection
    - Increased crypt depth and villus height
    - Increased intestinal blood flow
    - Increased absorptive capacity

Native GLP-2 has a half-life of only 7 minutes, limiting its clinical utility.

Butyrate-suppl PN ↑ plasma [GLP-2]

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SCFA</th>
<th>9Bu</th>
<th>60Bu</th>
</tr>
</thead>
</table>
| Plasma GLP-2 (pmol/L) | △ Control < SCFA Treatments, P = 0.007 | Barthsom et al., JPEN 2004;28:210-222.
**Teduglutide: A Recombinant GLP-2 Analog With Extended Half-life**

- Single amino acid substitution of alanine to glycine at the second position of the N-terminus
- Mean half-life of 1.3 hours in patients with SBS (vs 7 minutes for endogenous GLP-2)

Teduglutide is a prescription medicine administered as a daily subcutaneous injection for use in adults with SBS who need PN and/or IV fluids.


**Design of multicenter prospective, randomized, double-blind, placebo-controlled study**

- 83 PN-dependent subjects with intestinal failure
- Subjects
  - Optimize PN
  - Stabilize PN
  - Placebo (n=16)
  - Teduglutide 0.05 mg/kg/d (n=35)
- 24 wks
- Intestinal Biopsy

Jeppesen et al., Gastroenterol 2012;143:1473-1481.

**Representative change in small intestinal mucosa following 24 wks of 0.05 teduglutide administration.**

Baseline

End-of-study

Sustained, progressive PN reduction with longterm teduglutide use

Schwartz et al., Clin Transl Gastroenterol 2016;7: epub ahead of print.

Sustained, progressive results with longterm teduglutide use

Schwartz et al., Clin Transl Gastroenterol 2016;7: epub ahead of print.

Role of teduglutide and diet in a neonatal piglet model of SBS?

Jugular catheterization
80% jejunoileal resection

n = 72

TPN PEN (20%)
Vehicle TPN – PEN –
Teduglutide (0.1 mg/kg/d) TPN + PEN +
4h, 48h, 7d

Naberhuis et al., JPEN 2015;Aug 24, epub ahead of print.
Teduglutide and EN ↑ intestine villus height greater than either treatment alone.

Naberhuis et al., JPN 2015; Aug 24, e-pub ahead of print.

Representative mucosal architecture at 7d
Villus length numerically greatest in all segments.

Acknowledgements

Jen Barnes, Ph.D., R.D. NIDDK R01 DK 57682
Anne L. Bartholome, Ph.D., R.D. NPS Pharmaceuticals, Inc.
Jane Naberhuis, Ph.D.
Jens J. Holst, M.D., Ph.D.
Food in Children with Functional Abdominal Disorders: Does it Matter?

Nutrition Symposium
World Congress
Bruno Chumpitazi, MD, MPH
Kristi King

Disclosure

•Kristi King has no disclosures

•Bruno Chumpitazi has the following financial relationships to disclose:
  - QOL Medical LLC (research support)
  - Mead Johnson Nutrition (consultant)

•Products or services provided by these companies may be relevant to this presentation.

Objectives

1) Review the perspectives of patients re: food in functional abdominal pain and irritable bowel syndrome (IBS)

2) Use fermentable carbohydrates as a paradigm to explore the pathogenesis of food intolerance in IBS

3) Review host factors in IBS which may be related to food intolerance

4) Address barriers to low FODMAP/ nutrition based interventions
Diet in IBS: The Perspective From Our Patients

• Food is perceived to be a culprit by those with adult IBS in up to 84%.

• Children with IBS vs. Healthy Children (HC)
  - 143 of 154 (92.9%) IBS vs. 20/32 (62.5%) HC with one self-perceived food intolerance (P<0.001)
  - Culprit foods: 4 [2-6] IBS vs. 2 [0-4] HC (P<0.001)
  - Avoided foods: 2 [1-4] IBS vs. 0 [0-2.75] HC (P<0.001)

4Chumpitazi BP et al. J Acad Nutr Diet 2016; 116(9): 1458-64.
Diet in IBS: The Perspective From Our Patients

"I don’t eat at friends’ houses; I don’t trust her food. I bring my own."

-13 yo F with functional GI disorder

“You kind of feel left out because you want to be able to eat the same things they do, but don’t want to be that person at the party throwing up because of that.”

-16 yo F with functional GI disorder


Adverse Reactions to Food

Toxic

Non Toxic

Toxins

- Saxitoxin (shellfish)
- Vasoactive amines
  - Histamine (spoiled fish)


Non Toxic

Immunologic

- Food allergy
  - IgE mediated (wheat allergy)
  - Non-IgE mediated (celiac disease)
  - Nonceliac Gluten sensitivity

Adverse Reactions to Food

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2) Use fermentable carbohydrates as a paradigm to explore the pathogenesis of food intolerance in IBS
3) Review host factors in IBS which may be related to food intolerance
4) Address barriers to low FODMAP/ nutrition based interventions

FODMAP Carbohydrates
- Fermentable (bacterial metabolism)
- Oligosaccharides (fructans/galactans)
- Disaccharides (lactose)
- Monosaccharides (fructose)
- And
- Polyols (sugar alcohols - sorbitol)

• Poorly absorbed, osmotically active, rapidly fermented (produce gas)

FODMAP Hypothesis

Malabsorbed dietary carbohydrates

Physiologic effects
Osmotic load
Fermentable substrate
Luminal fluid
Luminal distention

Other effects?
Symptoms
Diarrhea
Bloating
Pain
Gas


FODMAP Summary Evidence Review

• Adult Irritable Bowel Syndrome (IBS)
  • 1 Double Blind Placebo Controlled Challenge Study
  • 4 Randomized Controlled Trials
  • Several uncontrolled studies (symptom improvement 56-94%)

• Pediatric IBS
  • One uncontrolled study (n=8, symptom improvement 50%)
  • 1 Randomized Cross-Over Trial

• Inflammatory Bowel Disease
  • Open-label studies

FODMAP Evidence Review

• Adult IBS – Double Blind Challenge Study

FODMAP Evidence Review
• Adult IBS – Randomized Crossover Trial (n=30)

Halmos EP et al. Gastroenterology 2014;146:67-75

FODMAP Evidence Review
• Healthy adults – Randomized Crossover Trial (n=8)

Halmos EP et al. Gastroenterology 2014;146:67-75

FODMAP Evidence Review
• Healthy Adults – Randomized Controlled Trial (n=37)

McIntosh K et al. Gut 2016 Mar 14 [Epub]
**FODMAP Evidence Review**

- Pediatric IBS – Randomized Crossover Trial (n=33)
  - 48 hour interventions; TACD=Typical American Childhood Diet

  ![Graph showing effects of TACD and low FODMAP diets](image)

  Chumpitazi BP et al. Aliment Pharm Ther 2015;42:418-27

**FODMAP Pathogenesis**

- Poorly Absorbed - Fructose

  ![Diagram illustrating fructose absorption](image)

  Biesiekierski JR. United European Gastroenterol J. 2014;2(1):10-13

- Lactose
  - Lactase
- Fructans/Galactans
  - Fructose/Galactose polymers
  - Lack human hydrolases
  - Essentially intact into colon
- Sugar alcohols
  - Sorbitol, Xylitol, Mannitol
  - Passive absorption

**FODMAP Evidence Review**

- FODMAP Evidence Review
  - Poorly Absorbed - Lactose
  - Fructans/Galactans
    - Fructose/Galactose polymers
    - Lack human hydrolases
    - Essentially intact into colon
  - Sugar alcohols
    - Sorbitol, Xylitol, Mannitol
    - Passive absorption

• Genetics of Lactase Expression

Curry A. Nature 2013;500:20-22

Campbell AK et al. Sci Prog 2009;92:241

- Similar overall frequency in IBS vs. healthy controls
- May vary within IBS subtypes

FODMAP Pathogenesis: Genetics

• Genetics of Lactase Expression


FODMAP Pathogenesis: Genetics

• Genetics of Sucrase-isomaltase Expression
  - Congenital (homozygous) sucrase isomaltase deficiency believed to be rare
  - Heterozygotes may have decreased sucrase and isomaltase activity\(^1,2\)
  - Preliminary results – SI Polymorphisms\(^3\)
    • Prevalence in FGID with pain (n=375): 2.67%
    • FGID with chronic diarrhea (n=375): 4.27%
    • Reference: 1.05-1.15%

1. Ament ME. J Pediatr 1973; 60:212-227

FODMAP Pathogenesis

• Osmotically active · Fructose

FODMAP Pathogenesis
• Osmotically active - Fructose


FODMAP Pathogenesis
• Osmotically active
  - Mannitol increases small bowel water content 10x versus glucose in healthy volunteers
  - Dietary FODMAP content correlates with ileostomy output
    • Higher output with higher FODMAP content
    - Enteral formulas with lower FODMAP content cause less enteral nutrition-associated diarrhea

1 Marciani L et al. Gastroenterology 2010;138:469-77
2 Barret JS et al. Aliment Pharmacol Ther 2010;31:874-882

FODMAP Pathogenesis
• Highly Fermentable

FODMAP Pathogenesis
• Highly Fermentable


---

FODMAP Pathogenesis
• Differences between IBS vs. Healthy Controls

Ong DK et al. J Gastroenterol Hepatol 2010;25:1366-1373

---

Gut Microbiome differs between IBS and Healthy Controls

FODMAP Pathogenesis

• Low FODMAP diet efficacy
  - ≥ 25% subjects do not improve

• Microbiome Composition Changes
  - Low FODMAP diet reduces luminal *Bifidobacteria*\(^1\)
  - Decreased relative abundance Clostridium cluster XIVa, *Akkermansia muciniphila*, *Ruminococcus*\(^2\)
  - Low FODMAP diet vs. habitual diet in children\(^3\)
  - Responders with different baseline composition

1Staudacher HM et al. J Nutr 2012;142:1510-1518

FODMAP Pathogenesis: Responders and Baseline Microbiome Composition

<table>
<thead>
<tr>
<th>OTU</th>
<th>Taxonomy</th>
<th>LDA (Log 10)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>2921213</td>
<td>Bacteroides (genus)</td>
<td>4.11</td>
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<tr>
<td>358781</td>
<td>Ruminococcaceae (family)</td>
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<tr>
<td>175441</td>
<td>Faecalibacterium prausnitzii (species)</td>
<td>3.53</td>
<td>.002</td>
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<td>178081</td>
<td>Ruminococcaceae (family)</td>
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<td>.025</td>
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<td>4446898</td>
<td>Bacteroides (genus)</td>
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<td>297057</td>
<td>Bacteroides (genus)</td>
<td>3.22</td>
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<td>4417335</td>
<td>Bacteroides (genus)</td>
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<td>.03</td>
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<tr>
<td>187505</td>
<td>Dorea (genus)</td>
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<td>.048</td>
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<tr>
<td>171559</td>
<td>Bacteroides (genus)</td>
<td>3.06</td>
<td>.05</td>
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<tr>
<td>4463532</td>
<td>Clostridiales (order)</td>
<td>2.86</td>
<td>.023</td>
</tr>
</tbody>
</table>

• *Bacteroides, Ruminococcaceae, F. prausnitzii, Dorea* with high saccharolytic potential


FODMAP Pathogenesis: Responders and Microbial Metabolic Potential

<table>
<thead>
<tr>
<th>KO</th>
<th>Pathway</th>
<th>LDA (Log 10)</th>
<th>P-value</th>
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<tr>
<td>K02529</td>
<td>LacI family transcriptional regulator</td>
<td>2.23</td>
<td>.028</td>
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<tr>
<td>K01209</td>
<td>Alpha-N-arabinofuranosidase</td>
<td>2.11</td>
<td>.045</td>
</tr>
<tr>
<td>K03496</td>
<td>Chromosome partitioning protein</td>
<td>2.03</td>
<td>.024</td>
</tr>
</tbody>
</table>

• LacI family transcriptional regulator
  - Regulate carbohydrate utilization genes
  - Allow expression of genes with substrate/environment changes

• Alpha-N-arabinofuranosidase
  - Arabinogalactans: galactans found in wheat flour

FODMAP Pathogenesis: Nonresponders and Baseline Microbiome Composition

<table>
<thead>
<tr>
<th>OTU</th>
<th>Taxonomy</th>
<th>LDA (Log 10)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>4558723</td>
<td>Bacteroides (genus)</td>
<td>2.8</td>
<td>.053</td>
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<tr>
<td>347529</td>
<td>Turicibacter (genus)</td>
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<td>.026</td>
</tr>
<tr>
<td>17859</td>
<td>Clostridiales (order)</td>
<td>2.6</td>
<td>.044</td>
</tr>
<tr>
<td>248902</td>
<td>Turicibacter (genus)</td>
<td>2.59</td>
<td>.015</td>
</tr>
</tbody>
</table>

• Uniquely enriched in *Turicibacter*
  - Fermentative capacity for grains given to animals
  - Decreased fructo-oligosaccharide fermentation capacity
  - T. sanguinis with limited carbohydrate capacity

• Enriched in bacteria unable to ferment FODMAPs

Microbiome Activity

• Microbiome has several activities with resultant metabolites (metabolome)
  - Degradation of undigested proteins and carbohydrates
    • Sugars, oligosaccharides, peptides, amino acids
    • Amino acids and monosaccharide fermentation
  - SCFAs, lactate, succinate, ethanol, hydrogen, carbon dioxide, amines, ammonia, phenols, indoles, thiols
  - Hydrogen disposal
    • Methane, hydrogen sulfide, acetate
  - Bile-acid transformation
    • Deconjugated bile acids, secondary bile acids

FODMAP Pathogenesis: Metabolomics

McIntosh K et al. Gut 2016 Mar 14 [Epub]
**Microbiome Related Pathogenesis: Short Chain Fatty Acids**

- SCFAs are a potential mechanism

  ![Diagram](Depoortere_I_Gut_2014_63_179-190)

**FODMAP Pathogenesis: Inflammation**

- Healthy Control
- Lactose Malabsorption
- Lactose Intolerance

![Image](Yang_J_et_al._Aliment_Pharmacol_Ther._2014_39_302-11)

**Food Intolerance Pathogenesis**

- Host Response: Visceral hypersensitivity

![Graph](Yang_J_et_al._Aliment_Pharmacol_Ther._2014_39_302-11)
Objectives

1) Review the perspectives of patients re: food in functional abdominal pain and irritable bowel syndrome (IBS)

2) Use fermentable carbohydrates as a paradigm to explore the pathogenesis of food intolerance in IBS

3) Review host factors in IBS which may be related to food intolerance

4) Address barriers to low FODMAP/ nutrition based interventions

Strategies for addressing barriers often encountered in low FODMAP diet implementation among children
Low FODMAP Diet

• A few rules to remember:
  - FODMAPs in the diet do not cause functional GI disorders but is an opportunity to minimize symptoms
  - This diet restricts FODMAP globally not individually
    • Reduce intake of ALL poorly absorbed short chain carbohydrates
  
Gibson & Shepherd. J Gastroenterol Hepatol. 2010

Low FODMAP Diet

• Remember this is a **LOW** FODMAP diet not a **NO** FODMAP diet

• No food is all GOOD or all BAD

• Diet changes should be made in the context of WHOLE diet

• Dietitian delivered diet in order to reach full potential of minimizing symptoms & meeting nutritional needs

Barriers/Limitations

• Strict eliminations can result in:
  - Weight loss
  - Food aversions
  - Failure to Thrive
  - Increased risk of nutrient deficiencies
  - Increased risk of eating disorders
Low FODMAP Diet - Implementation

• Full dietary recall
  - Assess frequency & volume of FODMAP intake

• Symptom history & record

• Adjust diet based on intake
  - Example: a patient is eating a large amount of beans (cultural diet); consider reducing intake prior to overwhelming family and completely eliminating from diet

• Target most problematic FODMAP containing foods
  - Partial restriction

Barriers/Limitations

• Complaints of constipation during elimination phase

• Restriction of prebiotic foods

• Role of small bowel bacteria overgrowth

• May be difficult for vegetarian patient

• Cut-off levels of FODMAP content

• FODMAP content of US-friendly foods

Low FODMAP Diet - Implementation

• Strict trial of Low FODMAP x 6-8 weeks
  - What’s REALISTIC?!

  • If symptoms continue, consider reduction of caffeine, alcohol*, high-fat foods

Most problematic per Barrett et al.

  - Oligosaccharides
    - Fructans – wheat, rye, onions, garlic, artichokes
    - Galactans – legumes
  - Disaccharides
    - Lactose – milk
  - Monosaccharides
    - Fructose – honey, apples, pears, watermelon, mango, & HFCS
  - Polyols
    - Sorbitol – apples, pears, stone fruit, SF mints/gum
    - Mannitol – mushrooms

Barrett & Gibson Therap Adv Gastroenterol 2012
Low FODMAP - Reintroduction

• Re-challenging/Reintroduction
  - Allows for individualization of diet
  - Avoids over-restriction

• Keeping track of symptoms while reintroducing is a vital part of the process

Low FODMAP Diet - Reintroduction

• Polyols ➔ Lactose ➔ Fructose ➔ Fructans ➔ Galactans
• Fructose ➔ Polyols ➔ Lactose ➔ Fructans ➔ Glucatans

• PICK A GROUP!

Low FODMAP Diet - Reintroduction

• 1 FODMAP per week

• Eat the food x2 that week

• If symptoms occur, remove food from diet
  - Once symptom free
    • Decrease serving size in half & challenge again
    • Try another food from within the same FODMAP group
Low FODMAP Diet - Reintroduction

UNIVERSITY OF ARIZONA PROTOCOL:

<table>
<thead>
<tr>
<th>Carbohydrate</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyols:</td>
<td></td>
</tr>
<tr>
<td>Sorbitol</td>
<td>2-4 dried apricots</td>
</tr>
<tr>
<td>Mannitol</td>
<td>½ cup mushrooms</td>
</tr>
<tr>
<td>Lactose</td>
<td>½ - 1 cup milk</td>
</tr>
<tr>
<td>Fructose</td>
<td>½ mango or 1-2 tsp honey</td>
</tr>
<tr>
<td>Fructans</td>
<td>2 slices of wheat bread, 1</td>
</tr>
<tr>
<td></td>
<td>garlic clove or 1 cup pasta</td>
</tr>
<tr>
<td>Galactans</td>
<td>½ cup lentils or chickpeas</td>
</tr>
</tbody>
</table>

Low FODMAP Diet

• High FODMAP food
  • Per serving

<table>
<thead>
<tr>
<th>Carbohydrate</th>
<th>Max Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>&lt;4 grams</td>
</tr>
<tr>
<td>Mannitol/Sorbitol (Polyols)</td>
<td>&lt;0.3 grams</td>
</tr>
<tr>
<td>Fructans</td>
<td></td>
</tr>
<tr>
<td>Galactooligosaccharides</td>
<td>&lt;0.3 grams</td>
</tr>
<tr>
<td>Fructans</td>
<td>&lt;0.3 grams</td>
</tr>
<tr>
<td>Fructose</td>
<td>&gt;0.2 grams excess of glucose</td>
</tr>
</tbody>
</table>

Barriers

• Poor consensus
• US foods
• Full restrictions

• Partial restrictions
• Don’t address food at all
Low FODMAP Diet

### Fructose

**High FODMAP**
- Green and yellow fruits
- Orange, grapefruit, tangerine, papaya, mango, and pineapple
- Watermelon, cantaloupe, honeydew, pineapple
- Peas, corn, lentils, chickpeas, green beans
- Brussels sprouts, cabbage, broccoli, cauliflower

**Substitute FODMAP**
- Blueberries, raspberries, strawberries, blackberries, mulberries
- Honey, agave

**Lactose**
- Whole milk, cheese, yogurt, ice cream
- Soft and fresh cheeses
- Rich in lactose

### Oligosaccharides

**High FODMAP**
- Flour, rice, potatoes, beans, lentils
- Asparagus, artichokes
- Green and yellow vegetables

**Substitute FODMAP**
- Carrots, celery, bok choy, bamboo shoots, eggplant, corn, green beans, lettuce, spinach, tomatoes, beans

### Polyols

**High FODMAP**
- Corn syrup, maltitol
- Sorbitol, mannitol, xylitol

**Substitute FODMAP**
- Carrots, celery, bok choy, bamboo shoots, eggplant, corn, green beans, lettuce, spinach, tomatoes, beans

### Proteins

**High FODMAP**
- Beef, chicken, fish, egg, tofu
- Almonds, flax, peanuts, pecans, sunflower seeds, walnuts, nut butters

**Substitute FODMAP**
- Fish, chicken, eggs, tofu
- Almonds, flax, peanuts, pecans, sunflower seeds, walnuts, nut butters

### Notes

- Portion size is important
- Some vegetables require limited intake due to moderate FODMAP concentration

---

**Charts adapted from:**
- Scarlata. 2010
- Gibson & Shepherd. 2009
- Mullin et al. 2014

---

**Low FODMAP Diet Probiotics**

**High FODMAP**
- Fermented foods: yogurt, kefir, kombucha
- Prebiotics: chicory, inulin, oligofructose

**Substitute FODMAP**
- Probiotics: lactobacillus, bifidobacterium

---

**Low FODMAP Diet Fiber**

**High FODMAP**
- Wheat, rye, oat bran, bran cereals
- Legumes, lentils, chickpeas
- Brussels sprouts, cabbage, broccoli, cauliflower

**Substitute FODMAP**
- Gluten-free bread, cereals, rice, corn, rice pasta, rice cakes

---

**Low FODMAP Diet Vitamins**

**High FODMAP**
- Fruits: watermelon, cantaloupe, honeydew, pineapple
- Vegetables: Brussels sprouts, cabbage, broccoli

**Substitute FODMAP**
- Fruits: blueberries, raspberries, strawberries, blackberries, bananas
- Vegetables: carrots, celery, bok choy, bamboo shoots
Focus on the FODMAP Friendly Snacks

- Vegetables
- Rice cakes
- Red meat
- Eggs
- Hard cheeses
- Popcorn

Focus on the FODMAP Friendly Beverages

- Water! Water! Water!
- Sodas w/ cane sugar
- Alternative milks
- Lactose free milk
- 125 mL fruit or vegetable juice (1 serving)

FODMAP Counseling

Additional Resources:

1) Monash University (www.med.monash.edu/cecs/fodmap)
   - iPhone and Android application
2) Shepherd Works
   - www.shepherdworks.com.au
   - The Low FODMAP Diet Cookbook
3) Publications
   - Barrett JS et al. Practical Gastroenterology 2007;31:51-65

Limitation: Lack of information on US foods
Take Home Points

• Diet related symptom generation is commonly perceived in children with IBS

• Food intolerance classically represents a non-immunologic adverse food reaction
  - Gas production and osmotic load play a role with FODMAPs
  - Microbiome composition and functional aspects are being elucidated

• Host factors such as genetics, inflammation, visceral sensitivity and neurohormonal responses to food may contribute to pathogenesis

Acknowledgements

• Children’s Nutrition Research Center
  - Robert Shulman
  - Danita Czyzewski
  - Mariella Self
  - Erica Weidler
  - Ann McMeans
  - Adetola Vaughan

• TCH GI Section and Motility Program

• Texas Children’s Microbiome Center
  - James Versalovic
  - Emily Hollister
  - Julia Cope

• Support
  - NASPGHAN Foundation
  - Texas Medical Center DDC (NIH DK56338)
  - NIDDK (K23 DK101688)
Introduction of Complementary Feeding: Lessons from Allergy and Celiac Disease Studies

Raanan Shamir, MD
Institute for Gastroenterology, Nutrition and Liver Diseases, Schneider Children’s Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Israel

I have the following financial relationships to disclose:

Nestlé: advisory board member, speaker
Danone: advisory board member, speaker
Abbott: advisory board member, speaker

No Products or services produced by this (these) company (companies) are relevant to my presentation.

Learning Objectives

Upon completion of this session, the learner will be able to:

1. Be familiar with Definitions and Concepts
2. Understand the reasoning behind the introduction of gluten (Celiac)
3. Understand the reasoning behind the introduction of allergenic foods
Definition

<table>
<thead>
<tr>
<th>COMPLEMENTARY FOODS</th>
<th>SOLID FOODS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant formula</td>
<td>MILK</td>
</tr>
<tr>
<td>Solid foods</td>
<td>Breast milk or infant formula</td>
</tr>
</tbody>
</table>

WHO

Prevalence and Reasons for Early Introduction of CF Variations by Milk Feeding Type

- 40.4% of mothers in the US (2005-2007), introduced solid foods before age 4 months.
- Prevalence varied by milk feeding type:
  - 24.3% BF
  - 52.7% FF
  - 50.2% Mixed


Current Practices
Introduction of CF in 5 EU Countries

- Solid food @ 4 mo:
  - 37% of FF
  - 17% of BF

Complementary feeding is introduced earlier than recommended in a sizeable number of infants, particularly among FF infants
LISA Birth Cohort

1st introduction of any solids
- 0-4 mo 32%
- 5-6 mo 49.3%
- >6 mo 18.8%

Solids diversity @ 4 mo
- No solid food 69.6%
- 1-2 groups 17.3%
- 3-8 groups 13.1%


Complementary feeding
Previous recommendations

<table>
<thead>
<tr>
<th></th>
<th>Solid foods</th>
<th>Cow's milk</th>
<th>Eggs</th>
<th>Peanuts</th>
<th>Fish</th>
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<tbody>
<tr>
<td>AAP 2000</td>
<td>&gt;4 mo</td>
<td>&gt;12 mo</td>
<td>&gt;24 mo</td>
<td>&gt;36 mo</td>
<td>&gt;36 mo</td>
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<tr>
<td>ASCIA 2006</td>
<td>&gt;4-6 mo</td>
<td></td>
<td>Option</td>
<td>Option</td>
<td></td>
</tr>
<tr>
<td>ACAAI 2006</td>
<td>&gt;12 mo</td>
<td>&gt;24 mo</td>
<td>&gt;36 mo</td>
<td>&gt;36 mo</td>
<td></td>
</tr>
</tbody>
</table>

Complementary feeding and Celiac Disease

Myleus A, et al. ESPGHAN 2007
JPEN 2009; 49:170-176
### PreventCD Project

**Hypothesis:**

Childhood celiac disease may be prevented

By introduction of gluten
- in small amounts
- 4-6 months of age
- preferably while being breastfed

---

Frequency of celiac disease was not significantly different between the 475 children who received 100 mg gluten and the 469 children who received placebo daily at age 16 - 24 weeks.


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Norris JM et al., JAMA 2005

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Norris JM et al., JAMA 2005

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Norris JM et al., JAMA 2005

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Norris JM et al., JAMA 2005

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Norris JM et al., JAMA 2005

---

Norris JM et al., JAMA 2005

---

Norris JM et al., JAMA 2005

---

Norris JM et al., JAMA 2005

---

Norris JM et al., JAMA 2005
Timing of Gluten introduction
Observational studies

Timing of Gluten introduction
RCT’s

Breast Feeding at Gluten Introduction
Interventional trials

Szajewska H and Shamir R. APT 2015
“...avoid both early (below 4 months) and late (7 or more months) introduction of gluten and introduce gluten while the infant is still breast-fed”

ESPGHAN Recommendations
2009

“Gluten can be introduced into the infant’s diet between the ages of 4 and 12 completed months.” Age of gluten introduction...in this age range does not seem to influence the absolute risk of developing CDA or CD during childhood” (conditional recommendation; depending on the age, quality of evidence varies from very low to high quality of evidence).”

“4 completed months = 17 weeks of age.

ESPGHAN Recommendations
2016

Allergy as a Model

- Attempts to reduce the risk for the development of allergy using dietary modification have generally focused on the delayed introduction or elimination of foods identified as potentially most allergenic

- There is also increasing interest in the active prevention of atopy using specific dietary components

ESPGHAN. JPGN 2016
Complementary feeding

Previous recommendations

<table>
<thead>
<tr>
<th></th>
<th>Solid foods</th>
<th>Cow's milk</th>
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<th>Peanuts</th>
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<td>&gt;24 mo</td>
<td>&gt;36 mo</td>
<td>&gt;36 mo</td>
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</tr>
</tbody>
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**Complementary Feeding & Allergy**

Table 1: Projected birth outcomes evaluating the effect of the introduction of solids on the development of allergies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Country</th>
<th>Allergies</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPSI (1991)</td>
<td>4,793</td>
<td>Germany</td>
<td>No evidence that delayed introduction of solid foods to 6 months or delayed introduction of cow's milk to 6 months prevents the development of allergies</td>
<td></td>
</tr>
<tr>
<td>Leedon (2008)</td>
<td>2,077</td>
<td>Germany</td>
<td>No evidence that delayed introduction of solid foods to 6 months or delayed introduction of cow's milk to 6 months prevents the development of allergies</td>
<td></td>
</tr>
<tr>
<td>FNS-A (2006)</td>
<td>2,578</td>
<td>The Netherlands</td>
<td>Delayed introduction of solid foods was associated with higher risk for aquapho, delayed introduction of other foods was associated with an increased risk for steps 4 and 5 years of age</td>
<td></td>
</tr>
<tr>
<td>Geraef-8 (2006)</td>
<td>1,915</td>
<td>The Netherlands</td>
<td>Delayed introduction of solid foods was associated with higher risk for aquapho, delayed introduction of other foods was associated with an increased risk for steps 4 and 5 years of age</td>
<td></td>
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</tbody>
</table>

Shamir R. The Nest 2013
**Early consumption of peanuts in infancy and peanut allergy**

Median monthly consumption in Israeli infants aged 8 to 14 months is 7.1 g of peanut protein, and it is 0 g in the UK (P < 0.001).

Median number of times peanut is eaten per month was 8 in Israel and 0 in the UK (P < 0.001).

The prevalence of PA in the UK was 1.85%, and the prevalence in Israel was 0.17% (P < 0.001).

---

**Prospsective Study of Peripregnancy Consumption of Peanuts or Tree Nuts by Mothers and the Risk of Peanut or Tree Nut Allergy in Their Offspring**

JAMA Pediatrics 2014

Randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age.

4 - 11 mo, skin prick test, excluding those with > 4 mm reaction

Positive test 1-4 mm

at least 6 g of peanut protein per week, distributed in three or more meals per week, until they reached 60 months of age or avoidance

---

**The LEAP Study**

Randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age.

4 - 11 mo, skin prick test, excluding those with > 4 mm reaction

Positive test 1-4 mm

2 g of peanut protein in a single dose and excluded if reacted

Incremental doses up to a total of 3.9 g and excluded if reacted

---
Conclusions

“The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.”

• "Do infants need to ingest 2 g of peanut protein (approximately 8 peanuts) X 3/wk on a regular basis for 5 years, or will it suffice to consume lesser amounts on a more intermittent basis for a shorter period of time?"

• "If regular peanut consumption is discontinued for a prolonged period, will tolerance persist?"

• "Can the findings of the LEAP study be applied to other foods, such as milk, eggs, and tree nuts?"


• Are there lessons to be learned from celiac disease?
The EAT Study

- Recruited, from the general population, 1303 exclusively BF infants, 3 months.
- Randomly assigned them to the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; early-introduction group) or to the current UK practice of exclusive BF to approximately 6 mo (standard introduction group).
- Primary outcome: food allergy to one or more of the six foods between 1 year and 3 years of age.

Early introduction, before 6 months of age, of at least some amount of multiple allergenic foods appears achievable and did not affect BF

Perkin et al. JACI 2016

Increased food diversity in the first year of life is inversely associated with allergic diseases

An increased diversity of CF introduced in the 1st year of life was inversely associated with asthma with a dose-response effect

A similar effect was observed for food allergy and food sensitization

Was associated with increased expression of markers for regulatory T cells

ESPGHAN, AAP and NIAID Recommendations

ESPGHAN and both the American Academy of Pediatrics (AAP) and the National Institute of Allergy and Infectious Diseases (NIAID) support:

- The introduction of solids between 4-6 months of age
- Avoiding delayed introduction of allergenic foods
Thank you for your kind attention.
Are we LEAPing in to and EATing disaster

Carina Venter PhD RD

I have the following financial relationships to disclose:

Nestle
Danone
Mead Johnson Nutrionals

No Products or services produced by this (these) company (companies) are relevant to my presentation.

Overview

• Pregnancy
• Breast feeding
• Early Life
The MOST important take-away points

• Prevention **DOES NOT EQUAL** management
  • It is two different worlds!
  • Like moving from the Isle of Wight to Cincinnati

Pregnancy
Development of the Human Immune System

- Development of thymus begins by 4w
- T"cells" populate thymus progenitor by 8w, mature by 12-13w
- T"cells" appear in peripheral blood, liver, spleen by 13-18w
- B"cells" appear in liver by 11-13w
- Circulating IgM ~ 17w

Immune system during pregnancy

- Mother and IgG is transferred across the placenta
- Maternal immunity may therefore have long term, perhaps even life long consequences for her infant.

Fetus

- Development of the foetal immune system starts very early on in pregnancy. Stem cells are present in the human yolk sac at 21 days of gestation, with the first lymphocyte seen in the thymus at the end of the ninth week of gestation. The lymphocytes can be seen in a range of organs, including the lungs and gut, from 14 weeks; and by 19–20 weeks, circulating B cells have detectable surface IgM.

The picture is so much bigger than this!
Maternal diet factor during pregnancy

Prebiotics
- no recommendations due to insufficient evidence

Probiotics
- Use recommended for reduced atopic dermatitis/eczema outcomes

Vitamin D
- Only preventative effect seems to be relating to wheeze. No recommendation at present apart from adequate intake.

Omega-3 long chain fatty acids
- Adequate intake is recommended at present, but more intervention trials are required.

Food allergen elimination/alteration
- Not recommended due to insufficient evidence

Healthy diet
- No clear associations and intervention trials are required

Palmer, Brown, Maslin and Venter Invited review Pediatr Allergy Immunol 2016

There is no substantial evidence at present to recommend that women modify their diet during pregnancy.

Breastfeeding

2001 WHO Recommendation

- Exclusive breast feeding for 6 months (vs. 4-6 months)
  (i.e., no introduction of solid foods)
- Reduction of gastrointestinal infections
  - No (further) reduction in respiratory infections or atopic disease
- In 2013 in the U.S., of the infants who were 19-35 months of age:
  - 76.5% were breastfed at birth,
  - 49.0% were breastfed at 6 months,
  - 27.0% were breastfed at 12 months,
  - 37.7% were exclusively breastfed at 3 months, and
  - 16.4% were exclusively breastfed at 6 months

Breast Milk

**Immune-regulating substances**
- Immunoglobulin A
- Oligosaccharides
- Long chain fatty acids...
- Cytokines
- Nucleotides
- Antioxidants
- Maternal immune cells
- Lactoferrin
- Lysozymes
- Dietary antigens
- Carotenoid levels

“Unlike infant formula, which is standardized within a very narrow range of composition, human milk composition is dynamic, and varies within a feeding, diurnally, over lactations, and between mothers and populations. Influences on compositional differences of human milk include maternal and environmental factors, and the expression and management of milk (e.g., its storage and pasteurization).”

Bernard et al. Allergy. 2014;69:888 97

Dietary antigens in breast milk

- B Lactoglobulin is found in the breast milk of up to 95% of mothers who ingest CM during lactation
- Peanut protein was detected in breast milk of 48% of lactating women after peanut ingestion.
- OVA was detected in breast milk of 75% of women in the egg group
- Intervention trials disappointing...


Breast Feeding

- Exclusive breast-feeding is recommended for at least 6 months and up to 24 months of age
- Partial breast feeding reduces the incidence of diarrhea, dysentery for children aged 2 years
- Breast feeding should continue beyond 2 years of age
- Dietary antigens in breast milk are not clear at the moment
- There is no need to avoid allergens during breast feeding

Fleischer et al. JACI IP 2013;1:29-36
When things go wrong..

COT (UK) report on peanut allergy (1998)

Pregnant or breast-feeding women who are themselves atopic, or where another first-degree relative of the child is atopic, may wish to avoid eating peanuts and peanut products during pregnancy and lactation.

Now withdrawn

http://cot.food.gov.uk/committee/committee-on-toxicity/cotreports/cotwgreports/cotpeanutallergy

Isle of Wight: Peanut allergy

<table>
<thead>
<tr>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
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</table>

COT report
Changes in sensitisation/clinical allergy to peanut

The overlap...

IgE mediated wheat allergy

- Introduction of wheat whilst breast feeding was associated with an increased risk of parent-reported wheat allergy.
- This finding was based on 16 children with parent reported wheat allergy, only four of whom had detectable levels of wheat-specific IgE on blood test.
- Also failed to control for a history of eczema in the child, which is likely to be associated with both dietary modifications and an increased risk of food sensitisation.

PIFA data from Southampton

- There was no statistically significant difference between groups for the age cow’s milk (in any form) was introduced into the diet.
- There was a statistically significant difference between the groups for concurrent feeding with cow’s milk in any form and breast milk (P = .015), suggesting that any concurrent feeding is beneficial.
- EAACI: Introducing potential food allergens while continuing to breastfeed may provide a reduced risk for development of food allergy.
- More recent data from the same cohort has shown that ‘concurrent breastfeeding with cows’ milk from any source’ was a risk factor for non-IgE mediated food allergy, but not for IgE-mediated food allergy.

Muraro et al. Allergy. 2014; 69:590-601

Just across the waters...

Timing of introduction of key food allergens to cows’ milk allergic (n = 22) and control groups (n =44). * significantly different between groups

Venter et al. 2016 Journal of Nutritional Health and Food Science in Press

Does milk introduction while breastfeeding prevent milk allergy?

- There was no difference for concurrent milk introduction between the two groups (CMA vs. no CMA) (p<0.16)
- There was no difference for concurrent milk introduction between the two groups (FA vs. no FA) (p<0.9)
- Significant predictors of CMA included: age of weaning, breast feeding duration and maternal food allergy (p<0.05)

Venter et al. 2016 Journal of Nutritional Health and Food Science in Press
Early life feeding
Healthy Eating and Solid Food Intake...

- Predominantly home cooked
- Low/negligent intake of highly processed "adult foods"
- Low use of commercial baby foods

Global implications: Advocating a healthy infant diet that is predominantly home cooked and provides high levels of fruits and vegetables might be a positive way to protect against food allergy development.


Commercial foods

Role of Food Diversity

- Finnish study: n= 3142 infants
  - By 3 to 4 months of age, food diversity was not associated with any of the allergic end points
  - By 6 months of age, less food diversity was associated with increased risk of allergic rhinitis but not with the other end points
  - By 12 months of age, less food diversity was associated with increased risk of any asthma, atopic asthma, wheeze, and allergic rhinitis

Isle of Wight – Diet Diversity

In participants with eczema at 3 months (OR 0.40, 95% CI 0.05-0.96; p = 0.046) and at 12 months (OR 0.65, 95% CI 0.39-1.07; p = 0.083), the higher the DD score at this age, the lower the risk of food allergy at age 3 years, but there was no association for food allergy outcome at age 10 years.

Changes in foods included: seen a dietitian vs. not

Following the dietetic consultation, the number of allergenic foods included in the infant’s diet increased significantly (p=0.003).

What did LEAP and EAT teach us?
NAIAD guidelines open for comment

<table>
<thead>
<tr>
<th>SPT</th>
<th>0-2 mm</th>
<th>3-7 mm</th>
<th>8 mm and above</th>
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</thead>
<tbody>
<tr>
<td>First feed</td>
<td>Give one dose at home/hospital</td>
<td>Start graded challenge in hospital (3.9 g protein)</td>
<td>Accept allergic...</td>
</tr>
<tr>
<td>Continued intake at home</td>
<td>2 g peanut protein, 3 x per week</td>
<td>2 g peanut protein, 3 x per week</td>
<td>avoid</td>
</tr>
</tbody>
</table>

Peanut Introduction/Challenge

- Graded introduction - hospital
- Peanut butter
  - Recommended to mix (smooth) peanut butter with hot water and cool it down — younger children
  - Can be mixed with fruit or vegetable purees
  - 5 doses: Give a total of approx. 3.9 g (approx. 3 ½ tsp.)
- Bamba
  - 39 sticks or mash up and mix with water
What does 2 g of peanut look like?

<table>
<thead>
<tr>
<th>Amount containing approximately 2 g of peanut protein</th>
<th>Bamba (17 g)</th>
<th>Peanut butter (20 g)</th>
<th>Peanuts (8 g)</th>
<th>Peanut flour (4 g)</th>
<th>Reese's cups (21 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 oz (50 g)</td>
<td>24 oz</td>
<td>8 oz</td>
<td>34 oz</td>
<td>12 oz</td>
<td>24 oz</td>
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<tr>
<td>15 oz (42 g)</td>
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Nutritional Composition of Peanut Butter Alternatives

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<th>Peanut flour (4 g)</th>
<th>Reese's cups (21 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat (g)</td>
<td>6.9</td>
<td>4.95</td>
<td>3.94</td>
<td>0.02</td>
<td>4.8</td>
</tr>
<tr>
<td>Sugar (g)</td>
<td>0.6</td>
<td>0.65</td>
<td>0.38</td>
<td>0.33</td>
<td>13</td>
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<tr>
<td>Salt (mg)</td>
<td>70</td>
<td>48</td>
<td>1</td>
<td>7</td>
<td>756</td>
</tr>
<tr>
<td>Kcals</td>
<td>91</td>
<td>59</td>
<td>45</td>
<td>15</td>
<td>210</td>
</tr>
</tbody>
</table>
| LEAP nutrition paper

EAT Study – what do amounts look like?

• 2g of each allergenic food protein per eating occasion x 2
  i.e. 4g protein per week.
• This equates to the following quantities per week:
  • Cow’s milk: Two small pots of yoghurt (40-60g) (4.86 /100g)
  • Sesame: 3 teaspoons of tahini (sesame paste) (2.55)
  • Wheat: 2 Weetabix or 40 grams dry pasta (5.22)
  • Egg: 1 small hardboiled egg (approx 5 egg white protein/egg i.e. 6 g)
  • Fish: 25 grams fish (5.1 g)
  • Peanuts: 3 teaspoons of peanut butter (3 g)

In Summary

• No need to change pregnancy diet
• No need to change diet during breast feeding
• Aim to breast feed for at least 4-6 months
• For interpretation of the LEAP and EAT study, look out for the international guidelines

Thank you!