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

Place d'Armes | Credit : © Tourisme Montréal, Stephan Poulin

CPNP

THE NASPGHAN COUNCIL FOR PEDIATRIC NUTRITION PROFESSIONALS

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CPNP

THE NASPGHAN COUNCIL FOR PEDIATRIC NUTRITION PROFESSIONALS

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

NASPGHAN Nutrition Symposium
CPNP Founders

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

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THE NASPGHAN COUNCIL FOR PEDIATRIC NUTRITION PROFESSIONALS

PROGRAM
October 7 – 8, 2016

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

Marialena 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 Tappenden, RD, PhD

Human Nutrition Endowed Professor, University of Illinois at Urbana-Champagne

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 available

11:30-12:30pm **Clinical Research Session**

INFLUENCE OF DIETITIANS IN PREVENTING PARENTERAL NUTRITION PRESCRIPTION ERRORS IN A PAEDIATRIC SETTING. Millie Garg[1], Michael Swab[2], Declan Gibney[2], Jennifer Cohen[1,2], Nitin Gupta[2], Chee (Keith) Y Ooi[1,2], [1]University of New South Wales, Randwick, New South Wales, Australia, [2]Sydney 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 Yamashiro[1], Ravinder Nagpal[1], Hirokazu Tsuji[2], Takuya Takahashi[2], Koji Nomoto[2], Kazunari Kawashima[3], Satoru Nagata[4], [1]Juntendo University School of Medicine, Bunkyo-ku, Tokyo, Japan, [2]Yakult Central Institute, Kunitachi, Tokyo, Japan, [3]Gonohashi Obstetrics & Gynecology Hospital, Koto-ku, Tokyo, Japan, [4]School of Pediatrics Medicine, Tokyo Women'sMedical 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

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

THE OHIO STATE UNIVERSITY

Disclosures

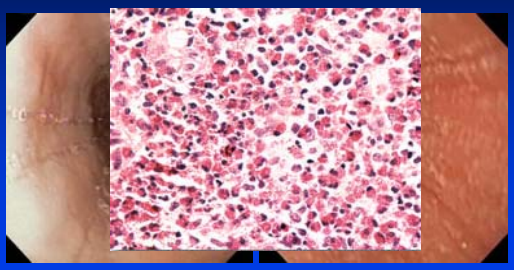
No disclosures or conflicts of interest related to this presentation

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

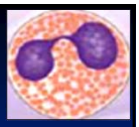
Find first what the problem is

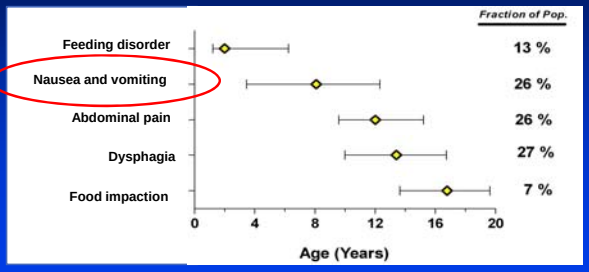
If you look for what is causing the early satiety, nausea, vomiting….

You may find this



Symptoms of Eosinophilic Esophagitis by age*





*Median and inter-quartile range, n=103

Or you may find duodenal eosinophilia (if you biopsied): Is it relevant?

Activated duodenal mucosal **eosinophils** in children with **dyspepsia**: a pilot transmission electron microscopic study.
Friesen CA, Andre L, Garola R, Hodge C, Roberts C.
J Pediatr Gastroenterol Nutr. 2002 Sep;35(3):328-33.

Clinical efficacy and pharmacokinetics of montelukast in dyspeptic children with **duodenal eosinophilia**.
Friesen CA, Kearns GL, Andre L, Neustrom M, Roberts CC, Abdel-Rahman SM.
J Pediatr Gastroenterol Nutr. 2004 Mar;38(3):343-51.

Mucosal **eosinophilia** and response to H1/H2 antagonist and cromolyn therapy in pediatric **dyspepsia**.
Friesen CA, Sandridge L, Andre L, Roberts CC, Abdel-Rahman SM.
Clin Pediatr (Phila). 2006 Mar;45(2):143-7.

A pilot study to assess the efficacy of biofeedback-assisted relaxation training as an adjunct treatment for pediatric functional **dyspepsia** associated with **duodenal eosinophilia**.
Schurman JV, Wu YP, Grayson P, Friesen CA.
J Pediatr Psychol. 2010 Sep;35(8):837-47. doi: 10.1093/jpepsy/jsp010. Epub 2010 Feb 25.

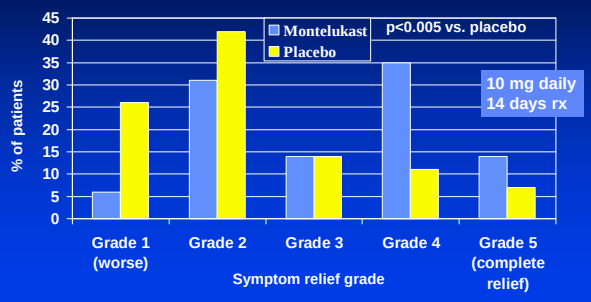
Non-ulcer **dyspepsia** and **duodenal eosinophilia**: an adult endoscopic population-based case-control study.
Talley NJ, Walker MM, Aro P, Ronkainen J, Storskrubb T, Hindley LA, Harmsen WS, Zinsmeister AR, Agréus L.
Clin Gastroenterol Hepatol. 2007 Oct;5(10):1175-83. Epub 2007 Aug 7.

Implications of **eosinophilia** in the normal **duodenal** biopsy - an association with allergy and functional **dyspepsia**.
Walker MM, Salehian SS, Murray CE, Rajendran A, Hoare JM, Negus R, Powell N, Talley NJ.
Aliment Pharmacol Ther. 2010 Jun;31(11):1229-36. doi: 10.1111/j.1365-2036.2010.04282.x. Epub 2010 Mar 4.

Montelukast in dyspeptic children with duodenal eosinophilia

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

Friesen CA, at al. J Pediatr Gastroenterol Nutr 2004;38:343-51



More tests?

Nuclear Medicine

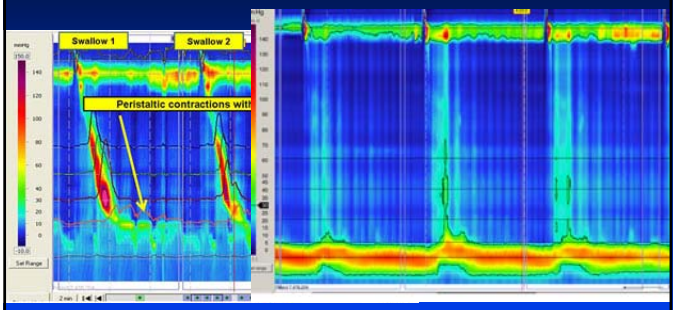
Pediatric normal values?

Abell TL et al. J Nucl Med Technol. 2008;36:44-54

- 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

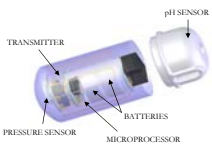
(JPGN 2013;56: 439–442)

Ashish Chogle and Miguel Saps

- 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



SmartPill

Wireless Motility Capsule Tracing- Gastroparetic Child

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLE

J Pediatr. 2013;162:1181-7

Wireless Motility Capsule Test in Children with Upper Gastrointestinal Symptoms

Alex D. Green, DO[1,*], Jaime Belkind-Gerson, MD[2,*], Brian C. Surjanhata, BS[3], Hayat Mousa, MD[1], Braden Kuo, MD[3], and Carlo Di Lorenzo, MD[1]

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

Getting tissue

Journal of Pediatric Gastroenterology and Nutrition
33:54–57 © July 2001 Lippincott Williams & Wilkins, Inc., Philadelphia

Laparoscopic Full-Thickness Intestinal Biopsies in Children

Mark V. Mazziotti and Jacob C. Langer

Department of Surgery, Division of Pediatric Surgery Washington University School of Medicine, St. Louis, Missouri, U.S.A.

ORIGINAL ARTICLE: Clinical Endoscopy

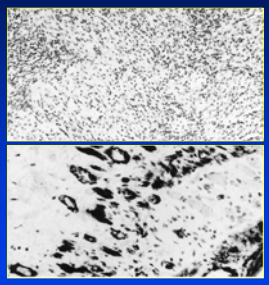
Gastrointest Endosc 2011;73:949-54

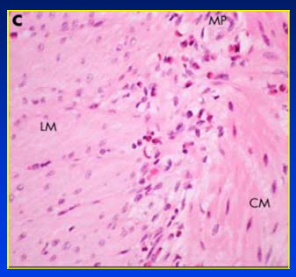
Percutaneous endoscopically assisted transenteric full-thickness gastric biopsy: initial experience in humans

Christopher N. Andrews, MD, MSc, FRCPC, Paul Mintchev, Emil Neshev, MD, Hughie F. Fraser, MD, FRCPC, Martin Storr, MD, Oliver F. Bathe, MD, FRCSC, Stefan J. Urbanski, MD

Calgary, Alberta, Canada

Myositis and eosinophilic ganglionitis





(Ruuska TH, Gastroenterology 2002; Schäppi MG, Gut 2003)

Treatments

Prokinetics?

Erythromycin

In patients with poor motility:

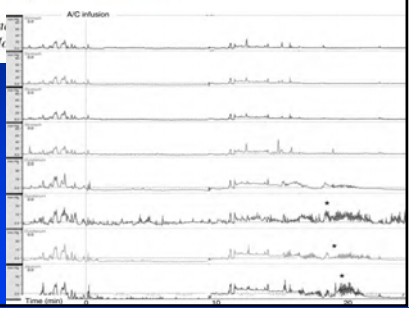
Use high doses

ORIGINAL ARTICLE: GASTROENTEROLOGY

JPGN 2012;54: 780–784

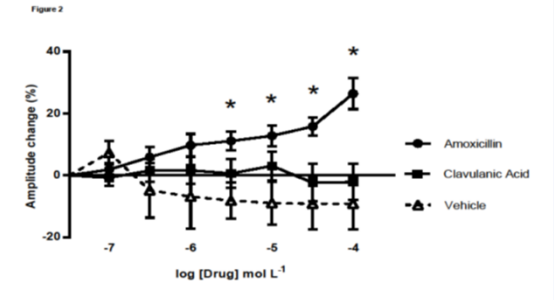
Effect of Amoxicillin/Clavulanate on Gastrointestinal Motility in Children

Roberto Gomez, Sergio Ferm
Hayat M



Intraduodenal 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]

Original article

doi:10.1111/j.1463-1318.2009.01838.x

The efficacy of treatment of patients with severe constipation or recurrent pseudo-obstruction with pyridostigmine

C. J. O'Dea, S. J. H. Brookes and D. A. Wattchow Colorectal Disease 2010 12, 540–548

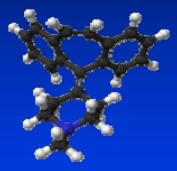
Departments of Surgery and of Human Physiology, Flinders Medical Centre and Flinders University, Bedford Park, South Australia

10 mg BID starting dose	Slow transit constipation	Intestinal pseudo-obstruction
Number of patients (% of total)	6 (42.85)	7 (57.15)
Age (years)	24–59	22–80
Gender		
Men	0	3
Women	6	4
Improvement with pyridostigmine (% of group)	1/6 (16.67)	7/7 (100)
Surgery (% of group)	5/6 (83.33)	2/7 (28.57)

Working on sensation and accomodation…

Old but good…

Cyproheptadine



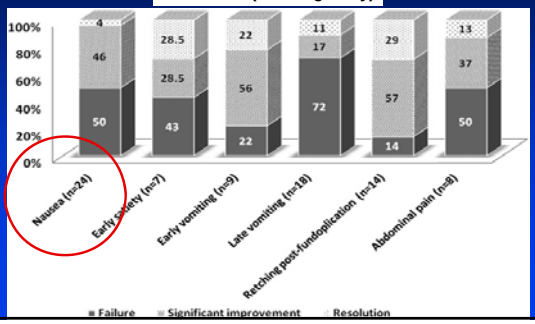
First generation anti-histamine with additional anticholinergic, antiserotonergic, and local anesthetic properties

Safety and Efficacy of Cyproheptadine for Treating Dyspeptic Symptoms in Children

J Pediatr 2013 (in press)

Leonel Rodriguez, MD, MS[1], Juan Diaz, MD, PhD[1,2], and Samuel Nurko, MD, MPH[1]

80 children (mean age 10 y)



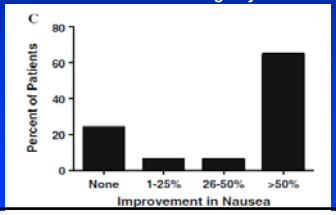
Clin Auton Res (2011) 21:419–423
DOI 10.1007/s10286-011-0130-x

SHORT COMMUNICATION

Fludrocortisone improves nausea in children with orthostatic intolerance (OI)

John E. Fortunato · Hossam A. Shaltout · Megan M. Larkin · Peter C. Rowe · Debra I. Diz · Kenneth L. Koch

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

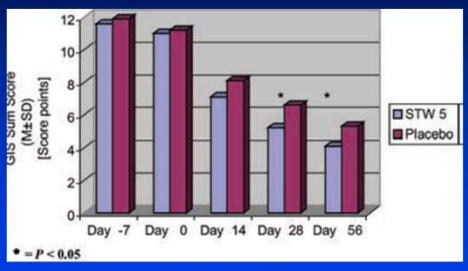


Iberogast

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.**

Iberogast in Functional Dyspepsia

von Arnim U, et al. Am J Gastroenterol. 2007;102:1268-75



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

Hypnotherapy for nausea?

RICHARDSON J., SMITH J.E., MCCALL G., RICHARDSON A., PILKINGTON K. & KIRSCH I. (2007) *European Journal of Cancer Care* **16**, 402–412
Hypnosis for nausea and vomiting in cancer chemotherapy: a systematic review of the research evidence

To systematically review the research evidence on the effectiveness of hypnosis for cancer chemotherapy-

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?

NIH Public Access
Author Manuscript
Cochrane Database Syst Rev. Author manuscript; available in PMC 2011 June 13.

Published in final edited form as:
Cochrane Database Syst Rev. ; (2): CD003281. doi:10.1002/14651858.CD003281.pub3.

Stimulation of the wrist acupuncture point P6 for preventing

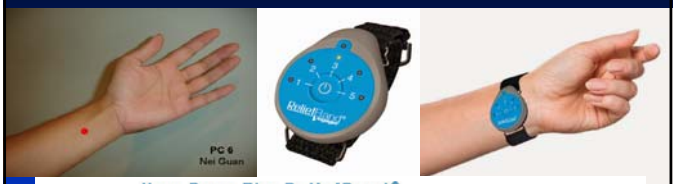
Authors' conclusions: P6 acupoint stimulation prevented PONV. There was no reliable evidence for differences in risks of postoperative nausea or vomiting after P6 acupoint stimulation compared to antiemetic drugs

alternative approach is to stimulate the P6 acupoint on the wrist. This is an update of a Cochrane review first published in 2004.

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

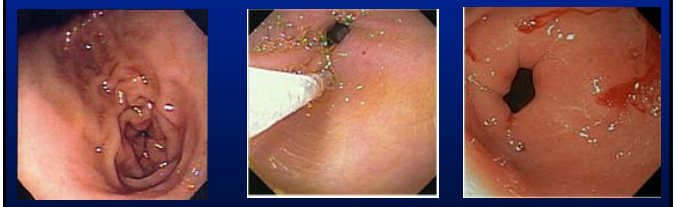
Search strategy—We searched CENTRAL (*The Cochrane Library*, Issue 3, 2008), MEDLINE (January 1966 to September 2008), EMBASE (January 1988 to September 2008), ISI Web of Science (January 1965 to September 2008), the National Library of Medicine publication list of acupuncture studies, and reference lists of articles.

The ReliefBand



More invasive treatments

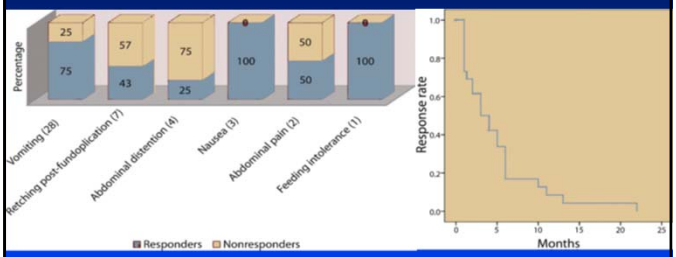
Botulinum Toxin:
100-200 Units divided in 4 quadrants



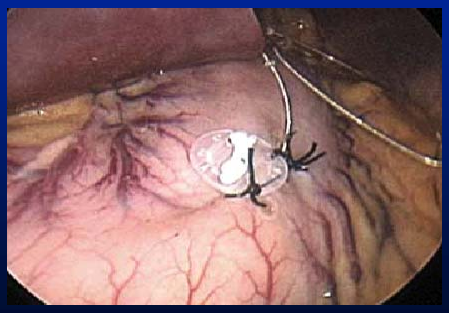
Endoscopic intrapyloric injection of botulinum toxin A in the treatment of children with gastroparesis: a retrospective, open-label study (CME)

Leonel Rodriguez, MD, MS, Rachel Rosen, MD, MPH, Michael Manfredi, MD, Samuel Nurko, MD, MPH

Gastrointest Endosc. 2012 Feb;75:302-9



Gastric Electrical Stimulation (GES): The nausea Holy Grail in pediatrics?



Journal of Pediatric Surgery (2013) 48, 178–183

Journal of Pediatric Surgery

www.elsevier.com/locate/jpedsurg

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]

Neurogastroenterology & Motility

Neurogastroenterol Motil (2013)

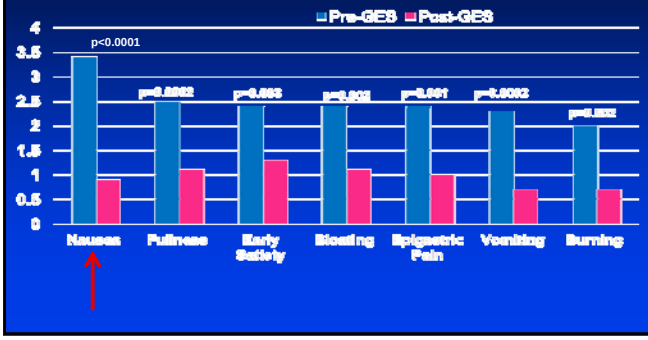
doi: 10.1111/nmo.12104

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

P. L. LU,* S. TEICH,† C. D. LORENZO,* B. SKAGGS,* M. ALHAJJ* & H. M. MOUSA*

Symptom Severity

Improved total score (p<0.0001)



Nutritional Aspects of Managing the Patient with Gastroparesis (GP)/Motility Disorders

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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

Waseem S, et al. J Pediatr Gastroenterol Nutr. 2012;55(2):166-72.

University of Virginia Health System Digestive Health Center

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!

Common Nutritional Concerns

- Vitamin D
  - 25-OH vitamin D
- Iron studies including:
  - Ferritin in *non-acute* phase setting
- Glucose
  - Check $HgbA_1C$ if DM present or suspected
- Folate
- B_{12}
  - Serum B12, methylmalonic acid

B_{12} Deficiency

- Bacterial proteases inactivate intrinsic factor
  - Causes malabsorption of B_{12}
  - Captured by anaerobic bacteria in lumen
  - Can convert to physiologically inactive form
- Consider checking:
  - Both serum B_{12} and methylmalonic acid
  - CBC for MCV (megaloblastic anemia)
- AAFP recommends empiric treatment if B_{12} < 400pcg/dL w/ clinicial signs/sx

Nutrition Intervention

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

Homko CJ, et al. Neurogastroenterol Motil 2015;27:501-508.

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 > lowfat solid > high-fat liquid > low-fat liquid

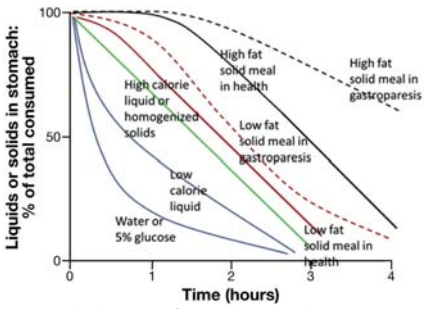
Olausson EA, et al. Am J Gastroenterol. 2014;109(3):375-85.
Homko CJ, et al. Neurogastroenterol Motil 2015;27:501-508.

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

Wytiaz V, et al. Dig Dis Sci 2015;60:1052-1058.

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.



Used with permission from Camilleri, Michael, M.D.

Camilleri M. Clin Gastroenterol Hepatol. 2016;14(8):1072-80.

Oral Diet Suggestions

- ↓ volume of meals
- ↑ frequency of meals
- ↓ 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

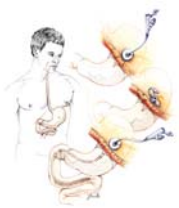
- Non-vented
  - Gastric
  - Nasoduodenal vs. nasojejunal
  - Direct Percutaneous endoscopic jejunostomy
  - Surgical or laparoscopic "J"
- Vented
  - Separate G and J ports
  - Jet-PEG (PEG/J)
    - (Jejunal extensions-12 Fr)

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

→ EDUCATION is *critical*



Enteral cont.

- Strict NPO during EN initiation (x 48 hrs^{+})
  - Nocturnal vs. continuous
  - If DM present:
    - Accucheks 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 glycemic 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)

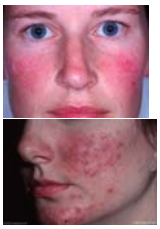
- At risk pts:
  - Short bowel syndrome with colon segment
  - Gastric bypass surgery for obesity
    - Diminished colonic motility can contribute
- Symptoms: altered mental status, slurred speech, ataxia, metabolic acidosis (can resemble alcohol intoxication)
- Check D-lactate (***not*** L-lactate)
  - 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

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General Gastroparesis

- Entire issue is dedicated to current understanding & management of gastroparesis:
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D-Lactic Acidosis

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SIBO & Rosacea

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

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SickKids
THE 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)

	First generation	Second generation		Third generation	
Abbreviation	Intralipid 20% SO	ClinOleic 20% OO/SO	Lipofundin 20% MCT/SO	SMOFlipid 20% multicomponent FO-containing	Omegaven 10% FO
Year of introduction	1960s	1990s	1980s	2000s	1990s
	Oil source, %				
Soya bean	100	20	50	30	0
MCT	0	0	50	30	0
Olive	0	80	0	25	0
Fish	0	0	0	15	100
	Fatty acids (% of total fatty acid)				
Linoleic acid	53	18.7	29.1	37.2	4.4
Arachidonic acid	0.1	0.5	0.2	1.0	2.1
α-Linolenic acid	8	2.3	4.5	4.7	1.8
Eicosapentaenoic acid	0	0	0	4.7	19.2
Docosahexaenoic acid	0	0	0	4.4	12.1
n-6:n-3 ratio	7:1	9:1	7:1	2.5:1	1:8
Phytosterols (mg/L) based on Angsten et al (39)*	348±33	237 ± 8	NA	47.6	0
Phytosterols (mg/L) based on Xu et al (27)†	439.07 ± 5.72	274.38 ± 2.60	278.14 ± 5.09	207	No phytosterols, squalene 26.7 mg/L
α-Tocopherol (mg/L)	38	32	85 ± 20	200	150–296

Hojsak et al. J Pediatr Gastroenterol Nutr 2016

Intestinal Failure Associated Liver Disease (IFALD)

- Incidence

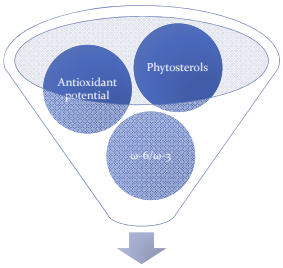
Setting	Incidence
Overall	30%
ELBW/VLBW on PN	25%
Term infants/children without IF	35%
Pediatric patients with IF	50%

- Histologically:
  - Cholestasis
  - Steatosis
  - Inflammation
  - Fibrosis

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

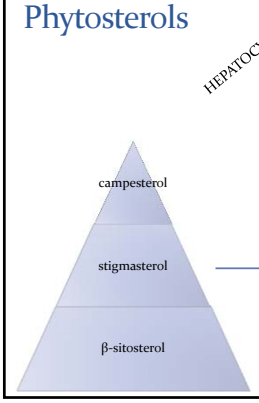
Rangel et al. J Pediatr Surg 2012;
Lauriti et al J Parent Enteral Nutr 2014
Sea Lee et al. J Pediatr 2015;
Nandivada et al. Am J Clin Nutr 2016

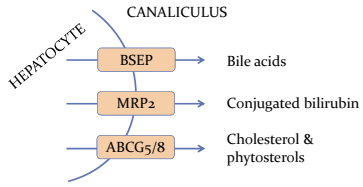
Pathogenesis: lipid emulsion contribution



IFALD

Phytosterols



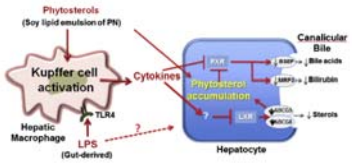


LXR and FXR antagonism:
- ↓Abcg5/8 expression
- ↓Abcb11 (BSEP), Abcc2 (MRP2) expression

Liver injury severity correlates with stigmasterol concentration in serum and liver

El Kasmi et al Sci Transl Med 2013

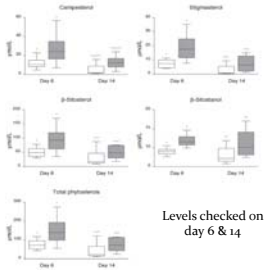
IFALD pathogenesis



Lee & Sokol. J Pediatr 2015

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

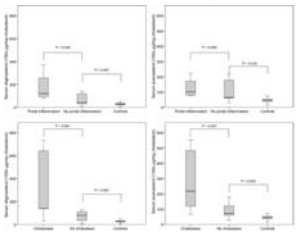


Levels checked on day 6 & 14

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

Savini et al. Am J Clin Nutr 2013;
Vlaardingerbroek et al. J Pediatr Gastroenterol Nutr 2014

Phytosterols in IFALD correlate with histology

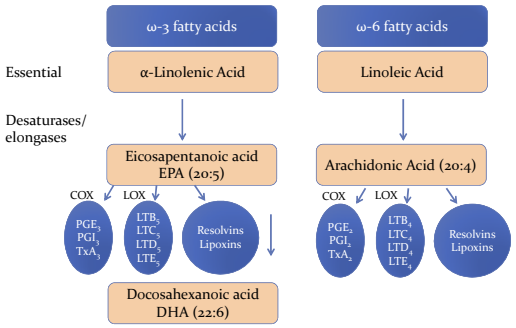


Cross-sectional study:
- Subjects on PN (n=16)
- Subjects previously on PN (n=34)
- Healthy controls (n=86)

In another study of pediatric IF patients, n=7 on PN and n=9 off PN:
- All PS fractions correlated with portal inflammation
- Fibrosis correlated with hepatic stigmasterol and campesterol levels

Mutanen et al. Am J Clin Nutr 2014;
Hukkinen et al. J Parent Enteral Nutr 2016

Essential Fatty acids



Significant variation in ω3/ω6 content of available LE

Abbreviation Year of introduction	Intralipid 20% SO 1960s	ClinOleic 20% OO/SO 1990s	Lipofundin 20% MCT/SO 1980s	SMOFlipid 20% multicomponent FO-containing 2000s	Omegaven 10% FO 1990s
	Oil source, %				
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α-Tocopherol (mg/L)	38	32	85 ± 20	200	150–296

PUFA → peroxidation → ROS → oxidative stress
- Cholestasis secondary to poor bile flow

Hojsak et al. J Pediatr Gastroenterol Nutr 2016
Roma & Sanchez-Pozi, Ann Hepatol 2009

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 ≥ 1 month

Variable	First value	Last value	*P* value
ALA, 18:3n−3 (μmol/L)	143.4 ± 114.5[2]	58.0 ± 39.8	<0.0001[3]
EPA, 20:5n−3 (μmol/L)	53 (35–74)[4]	644 (294–1046)	<0.0001[5]
DHA, 22:6n−3 (μmol/L)	170 (114–280)	750 (504–986)	<0.0001[5]
LA, 18:2n−6 (μmol/L)	2750.9 ± 1219.1	1618.0 ± 652.9	<0.0001[3]

Diamond et al. J Parenter Enteral Nutr 2016;
Le et al. Am J Clin Nutr 2011

Markers of lipid peroxidation in children with IFALD

Study	Cohort	Design	Dose/Duration	Outcome
Goulet et al.	Home PN	RCT IL® vs. SMOF®	2 g/kg/d 29 days	No difference in lipid peroxidation markers
Skouroliakou et al	<32 GA or Bwt<1500g	RCT IL® vs. SMOF®	2.3 g/kg/d 21-49 days	↓oxidative stress with SMOF®
Deshpande et al	<30 GA	RCT Clinoleic® vs. SMOF®	7 days	↓lipid peroxidation and ↑EPA with SMOF®
D'Ascenzo et al.	<1250 g	RCT Lipofundin® vs. SMOF®	1.7-1.8 g/kg/d 7 days	↑DHA, EPA and ↓AA with SMOF®

Goulet et al. J Parenter Enteral Nutr 2010;
Skouroliakou et al. Eur J Clin Nutr 2010;
Deshpande et al. J Pediatr Gastroenterol Nutr 2014;
D'Ascenzo et al. J Pediatr 2011;

Vitamin E

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

Abbreviation Year of introduction	Intralipid 20% SO 1960s	ClinOleic 20% OO/SO 1990s	Lipofundin 20% MCT/SO 1980s	SMOFlipid 20% multicomponent FO-containing 2000s	Omegaven 10% FO 1990s
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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

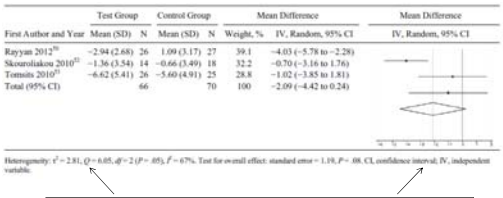
Hepatic outcomes using 3rd generation LE: **Combination lipids**

- 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

Finn et al. J Parent Enteral Nutr 2015

SMOF® may lead to lower total bilirubin in premature infants

- Total bilirubin assessed at ~2 weeks after PN initiation



First Author and Year	Test Group Mean (SD)	N	Control Group Mean (SD)	N	Mean Difference Weight, %	Mean Difference IV, Random, 95% CI
Rayyan 2012[28]	−2.94 (2.68)	26	1.09 (3.17)	27	39.1	−4.03 (−5.78 to −2.28)
Skouroliakou 2010[22]	−1.36 (3.54)	14	−0.66 (3.49)	18	32.2	−0.70 (−3.16 to 1.76)
Tomsits 2010[23]	−6.62 (5.41)	26	−5.60 (4.91)	25	28.8	−1.02 (−3.85 to 1.81)
Total (95% CI)		66		70	100	−2.09 (−4.42 to 0.24)

Mean Difference IV, Random, 95% CI

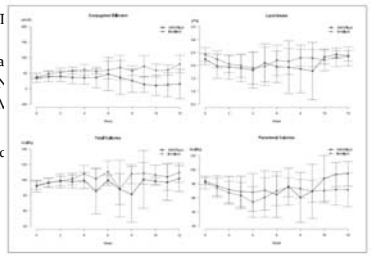
Heterogeneity: $\tau^2 = 2.81$, $Q = 6.05$, $df = 2$ ($P = .05$), $I^2 = 67\%$. Test for overall effect: standard error = 1.19, $P = .08$. CI, confidence interval; IV, independent variable.

SMOF®: **↓in TB by 2 mg/dL** (95% CI: -4.4 to 0.2; **p=0.08**)

Finn et al. J Parent Enteral Nutr 2015

SMOF® can prevent the progression of IFALD in neonates with IF

- RCT
- Infa
  - N
  - M
- Mec



SMOF® vs IL®

At study exit, CB>50 umol/L: 27% vs. 69% of patients

4 weeks post PN, CB>50 umol/L : 9% vs. 46% of patients

Diamond et al. J Parent Enteral Nutr 2016

Total bilirubin beyond the neonatal period

Goulet et al.	Muhammed et al	Pichler et al.
Home PN patients (total n=28)	Home PN patients (total n=17)	Older children (n=74) with TB>50 mg/dL or LE>2 ULN following 2 weeks on IL®
RCT: SMOF® vs. IL®	Retrospective: SMOF® vs. IL®	Retrospective: SMOF® vs. Lipofundin®
29 days; 2 g/kg/d	**6 months**;	**29 days** (median); 2.2 g/kg/d
TB change (mg/dL): SMOF® -0.09 vs. IL® +0.13	**TB change (mg/dL): SMOF® -5.9 vs. IL® +4.6**	**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

Lam et al. NASPGHAN 2015

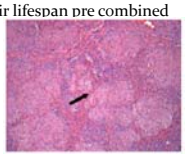
Fish oil based lipid emulsions

- 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 10, 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

Puder et al. Ann Surg 2009; Diamond et al. Pediatr Surg Int 2008; Nehra et al. J Parent Enteral Nutr 2014; Lam et al. Neonatol 2014 Seida et al. J Parent Enteral Nutr 2013

Biochemical improvement with fish oil does not correlate with fibrosis reversal

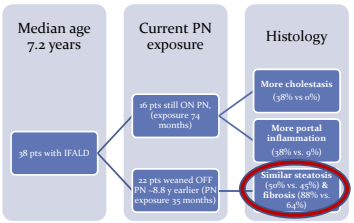
- 7 patients with IF on Omegaven® x ~ 62% of their lifespan pre combined liver/intestinal transplant
  - 6/7 patients with ultra-short gut
  - Fish oil introduced at 9 months
  - Fish oil exposure 16 months
    - 1 g/kg/d



  - 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

Matsumoto et al. J Pediatr 2014
Soden et al. J Pediatr 2010;
Mercer et al. J Pediatr Gastroenterol Nutr 2013

IFALD persists after PN cessation

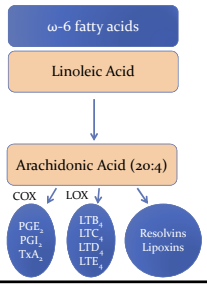


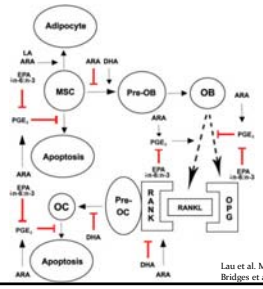
Mutanen et al. Hepatol 2013

Extrahepatic manifestations of prolonged exposure to lipid emulsions

Extrahepatic manifestations of LE: BONES

- PUFA affect differentiation and activity of bone cells
- In utero, 5:1 transport of AA:DHA to fetus during 3rd trimester





Lau et al. Molecules 2013;
Bridges et al. Nutr Rev 2015

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

Kruger et al. Prog Lipid Res 2010;
Kajarabille et al. Sci World J 2013;
Watkins et al. J Nutr 2000;
Lukas et al. Bone 2011;
Bridges et al. Nutr Rev 2015

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):

	Fish oil	Soybean oil
Incidence	5%	12%
Type of fx	17% ribs	67% extremities
Recurrent fx	29%	67%

Skouroliakou et al. Nutr Clin Pract 2012; Tomsits et al. J Pediatr Gastroenterol Nutr 2010; D'Ascenzo et al. Clin Nutr 2014; Fallon et al. J Surg Res 2014

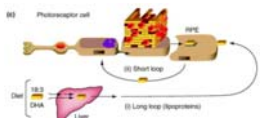
Extrahepatic manifestations of LE: BPD

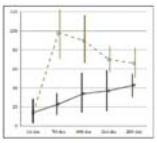
- Observational data suggesting lower incidence of BPD with SMOF® vs. IL® in VLBW infants
- Cochrane review on LE impact on preterm infants
  - Pooled effect towards decreased BPD with olive-soybean LE vs soybean LE – not statistically significant (n=261; studies=4)

Skouroliakou et al. Nutr Clin Pract 2012; Kapoor et al. Cochrane Database Syst Rev 2015

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 that soybean LE in preventing ROP stage 1-2 (NNTB=4) – associated with changes in RBC DHA
  - No difference in ROP ≥3

Bazan Trends Neurosci 2006; Kapoor et al. Cochrane Database Syst Rev 2015; Pawlik et al. J Parenter Enteral Nutr 2014;

Neurodevelopmental outcomes

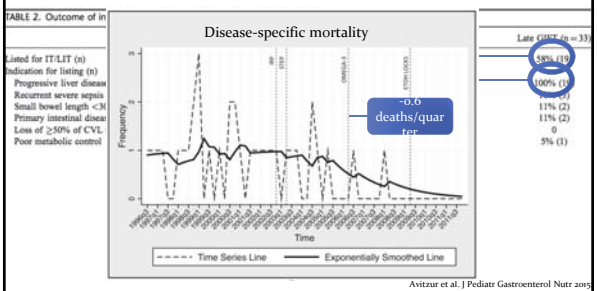
- Conflicting data re: impact of DHA supplementation of diets of premature infants on neurodevelopmental outcomes
- Limited data on impact of LE
- Differences in LE provision in infancy (dose, duration, EFAD) have no impact on neurocognitive assessment at 2-5 years of age
- Further research needed to determine the impact of different LE

Collins et al. BMJ Open 2015;
Auestad et al. Pediatr 2003;
Blackmer et al. J Parent Enter Nutr 2015;

Overall outcomes

Impact of LE on overall outcome

- Challenging to isolate LE effect – concurrent changes in care



Avitzur et al. J Pediatr Gastroenterol Nutr 2015
Stanger et al. J Pediatr Surg 2013;
Oliveira et al. J Am Coll Surg 2016

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.
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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:

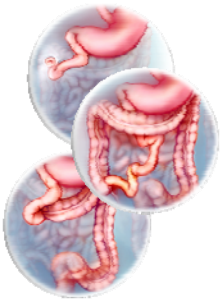
1. Describe the diagnostic criteria and treatment goals for patients with short-bowel syndrome (SBS)-associated intestinal failure (IF).
2. Outline the importance of driving intestinal rehabilitation in patients with SBS-IF.
3. Understand the latest therapeutic options available to patients with SBS-IF.

SBS-IF: A Complex and Life-Threatening Disorder[1]

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

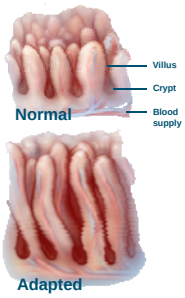
Extensive resection may cause malabsorption if the length and quality of the remaining small bowel is inadequate



Storch KJ. JPEN 2014;38:5S-7S.

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[5]



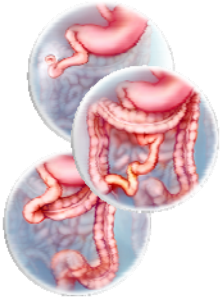
Tappenden KA. JPEN 2014:38:23S-31S.

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

Patients with SBS-associated IF are unable to maintain fluid and nutrient balances through a normal diet

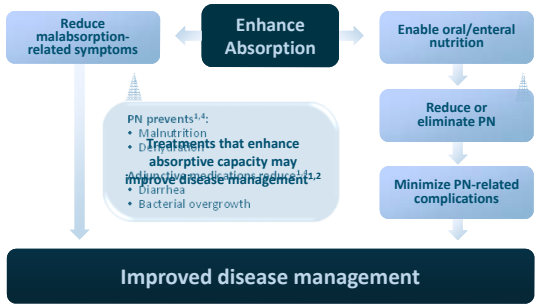
Patients with SBS-IF may become dependent on intravenous nutrient/fluid supplementation through parenteral nutrition (PN)

SBS-IF and PN-dependency is associated with many complications and reduced patient survival



Winkler MF, Smith CE. JPEN 2014:38:32S-37S.

Disease Management: Overview



Tappenden KA. JPEN 2014:38:23S-31S.

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 neurotensin
  - 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

Tappenden KA. Gastroenterol 2006;130(2 Suppl):S93-S99.
Seidner D, et al. JPEN 2013;37(2):201-211.

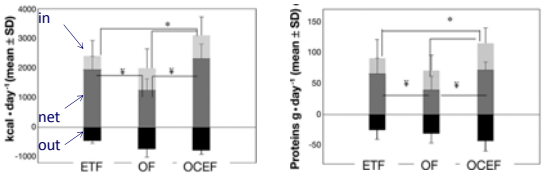
Enteral Nutrition (EN) in Children with Short-Bowel Syndrome

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.

Olieman JF, et al. JAND 2010;110:420-426.

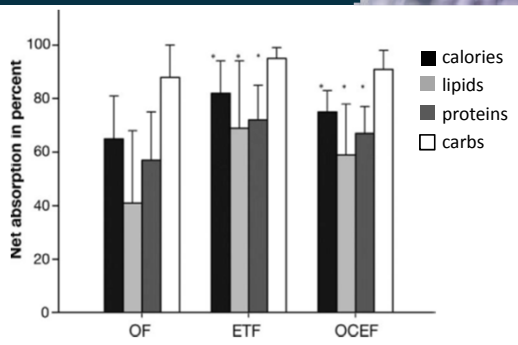
Tube Feeding ↑ Absorption in SBS-IF Patients

- 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 + 1000kcal/d tube (OCEF)
- ETF and OCEF ↑ net absorption of lipids, proteins, and energy compared with OF



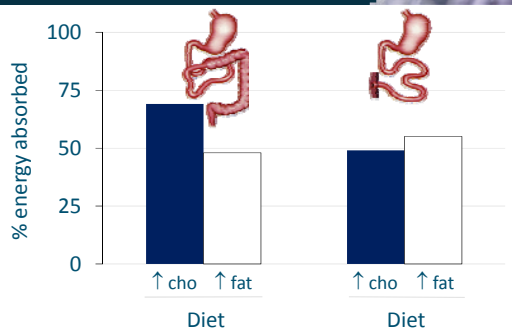
Joly F et al., Gastroenterology 2009;136(3):824-831.

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



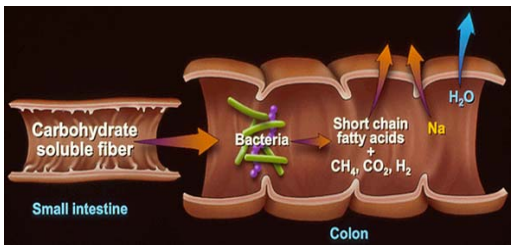
Joly et al., Gastroenterology 2009;136(3):824-831.

Energy absorption increased by functional colon and high carbohydrate diet



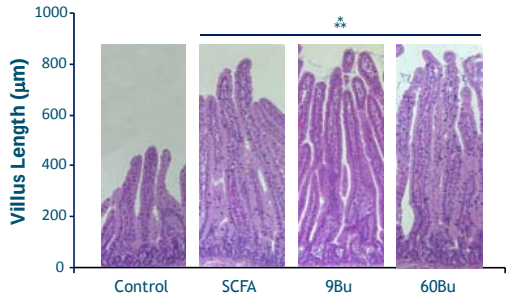
Nordgaard et al., Lancet 1994;343:373-376.

Colon 'important in the digestion of carbohydrates and hence in the salvage of calories in patients with SBS…'



Nordgaard et al., Lancet 1994;343:373-376.

Butyrate-supplemented PN increases ileal villous length



⁂ Control < SCFA groups, $P < 0.0001$

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 fructooligosaccharies (scFOS), a rapidly fermented prebiotic, may be a clinically efficacious means for delivering butyrate
- Synbiotic approach necessary?

Pre- and probiotics → SCFA: butyrate → Intestinal adaptation

Experimental design

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

n = 96

24h, 3d or 7d

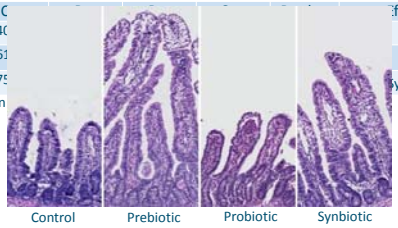
Control	Prebiotic	Probiotic	Synbiotic
20% EN/ 80% PN	10 g/kg BW FOS	$1x10^9$ CFU LGG	FOS + LGG

Barnes et al., JPEN 2012;36:524-537.

Ileal villus height ↑ by prebiotic treatment

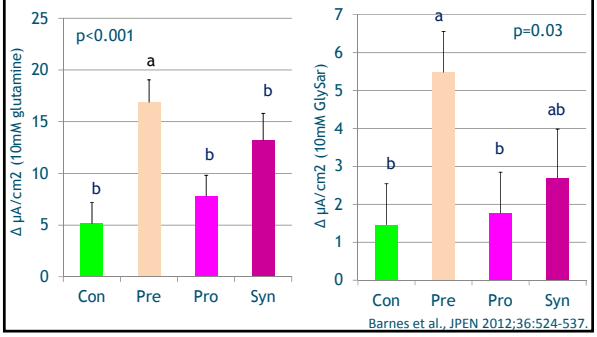
	Treatment			
	C			Effect
Duodenum	340			
Jejunum	361			
Ileum	375			Syn > Con

*Data presented in



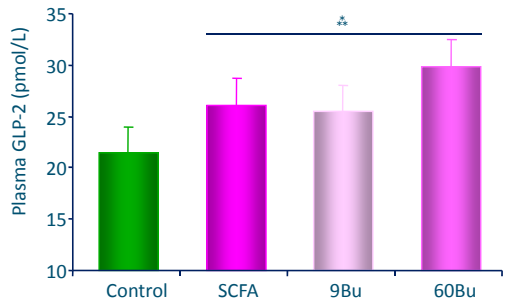
Barnes et al., JPEN 2012;36:524-537.

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



Barnes et al., JPEN 2012;36:524-537.

Butyrate-suppl PN ↑ plasma [GLP-2]

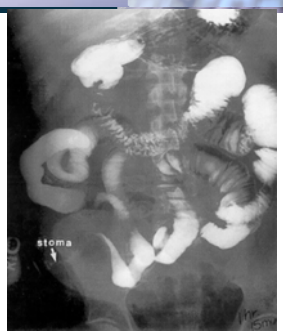


⁂ Control < SCFA Treatments, *P* = 0.007

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

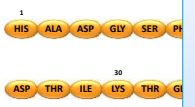
What about humans with intestinal failure?

Intact Gastrointestinal Tract



Short-Bowel Syndrome

Role of GLP-2 in Intes



Mucosal hyperplasia in GLP-2-treated murine small intestine[2]

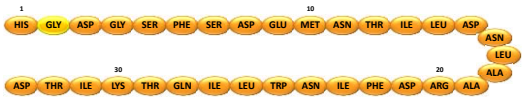
- Peptide hormone produ
- Induces local release of g
  subepithelial myofibrobl
- Evidence indicates GLP-2 tion[3-5]:
  - ↑ levels after resection
  - ↑ crypt depth and villus hei stimulates intestinal blood flow[2,3,4]
  - ↑ absorptive capacity[6]

Treatments that enhance absorptive capacity of the intestine may improve disease management[1,2]

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

Drucker et al., PNAS 1996;93:7911-7916

Teduglutide: A Recombinant GLP-2 Analog With Extended Half-life[1,2]

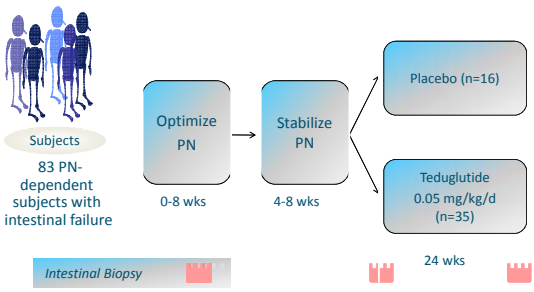


- Single amino acid substitution of alanine to glycine at the second position of the N-terminus
- Mean half-life of 1.3 hours in patients with SBS (vs 7 minutes for endogenous GLP-2)

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

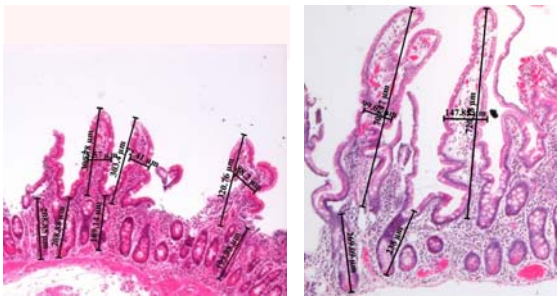
Marier et al., J Clin Pharmacol 2010;50:36-49.

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



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

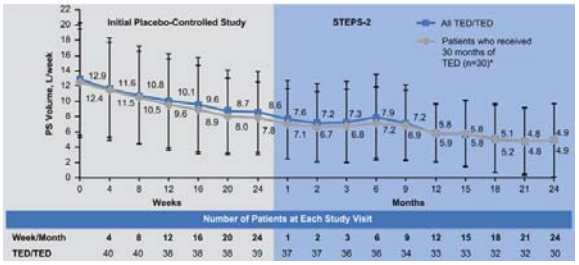
Representative change in small intestinal mucosa following 24 wks of 0.05 teduglutide administration.



Baseline End-of-study

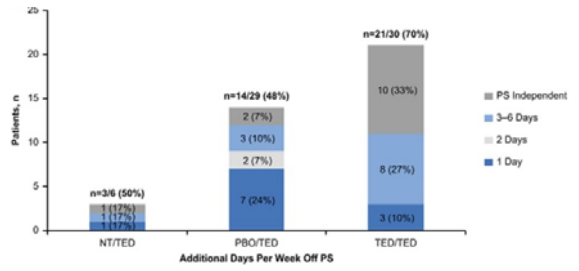
Tappenden et al., J Clin Gastroenterol. 2013. doi:10.1097/MCG.0b013e3182828f57

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

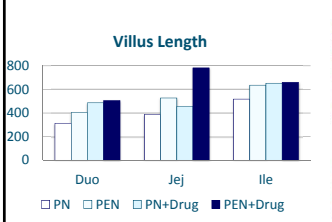
n = 72

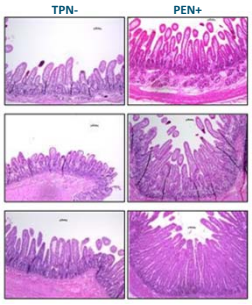
	TPN	PEN (20%)
Vehicle	**TPN –**	**PEN –**
Teduglutide (0.1 mg/kg/d)	**TPN +**	**PEN +**

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., JPEN 2015; Aug 24, *epub ahead of print*.

Representative mucosal architecture at 7d

PEN+ villus length numerically greatest in all segments

Acknowledgements

Jen Barnes, Ph.D., R.D.
Anne L. Bartholome, Ph.D., R.D.
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Jens J. Holst, M.D., Ph.D.

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Food in Children with Functional Abdominal Disorders: Does it Matter?

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

Disclosure

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- 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.

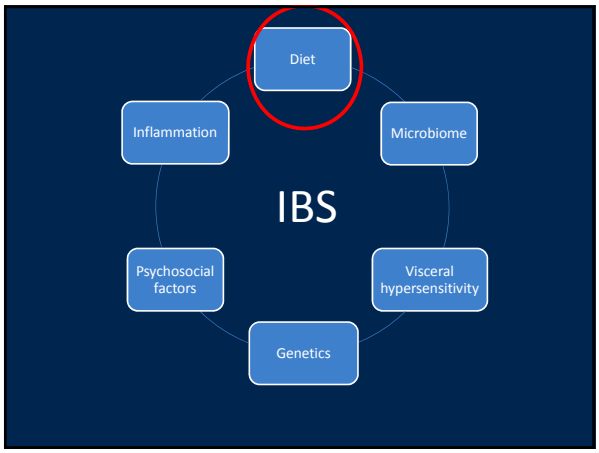
Objectives

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

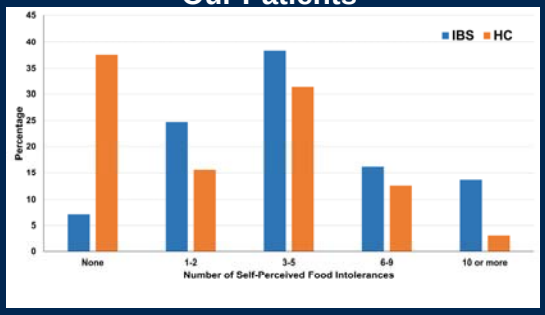


Diet in IBS: The Perspective From Our Patients

- Food is perceived to be a culprit by those with adult IBS in up to 84%[1]
- Children with IBS vs. Healthy Children (HC)[2]
  - 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)

[1]Bohn L et al. *Am J Gastroneterol* 2013; 108(5):634-41
[2]Chumpitazi BP et al. *J Acad Nutr Diet* 2016; 116(9): 1458-64.
[3]Carlson MJ et al. *J Acad Nutr Diet* 2014; 114(3):403-13

Diet in IBS: The Perspective From Our Patients



Chumpitazi BP et al. *J Acad Nutr Diet* 2016; 116(9): 1458-64.

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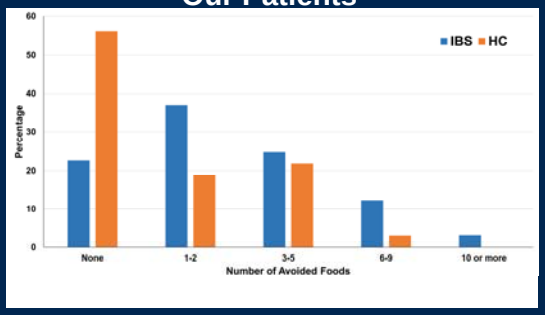


Chumpitazi BP et al. *J Acad Nutr Diet* 2016; 116(9): 1458-64.

Diet in IBS: The Perspective From Our Patients

Food or food type[a]	Children with IBS[b] (n = 154)	Healthy children (n = 32)
	n (%)	
Cow's milk	51 (33.1)	3 (9.4)
Fast food	37 (24)	3 (9.4)
Cheese	35 (22.7)	2 (6.3)
Ice cream	34 (22.1)	3 (9.4)
Spicy food	32 (20.8)	4 (12.5)
Beans	23 (14.9)	3 (9.4)
Pizza	23 (14.9)	1 (3.1)
Sodas	21 (13.6)	1 (3.1)
Chocolate	20 (13)	3 (9.4)
Fried foods	18 (11.7)	2 (6.3)

Chumpitazi BP et al. *J Acad Nutr Diet* 2016; 116(9): 1458-64.

Diet in Functional Pain: 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

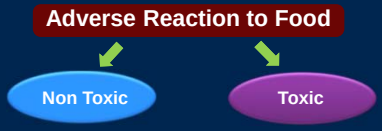
Carlson MJ et al. *J Acad Nutr Diet* 2014; 114:403-413.

Diet in IBS: The Prospective From Our Patients

Characteristic	Median value (25% to 75% quartile)	Spearman correlation *r* value	*P* value
Number of daily pain episodes[b]	1 (0.5-1.6)	0.17	<0.05
Median pain severity[b]	3.25 (2.3-4.0)	0.2	<0.05
Somatization[c]	24 (15-35.7)	0.22	<0.01
Anxiety (BASC-2[d] T-score)	51 (43-62)	0.21	0.01
Functional disability[e]	9 (4-19)	0.16	<0.05
Quality of life[f]	81.8 (70.7-89.1)	−0.17	<0.05
Depression (BASC-2 T-score)	45 (41-51)	0.1	0.2

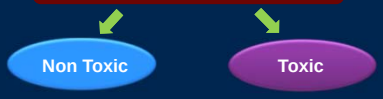
Chumpitazi BP et al. *J Acad Nutr Diet* 2016; 116(9): 1458-64.

Adverse Reactions to Food



Ortolani C et al. *Best Pract Res Clin Gastroenterol* 2006; 20(3):467-83.

Adverse Reactions to Food

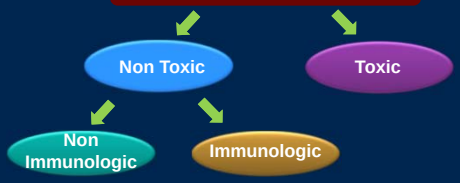


Toxins

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

Ortolani C et al. *Best Pract Res Clin Gastroenterol* 2006; 20(3):467-83.

Adverse Reactions to Food



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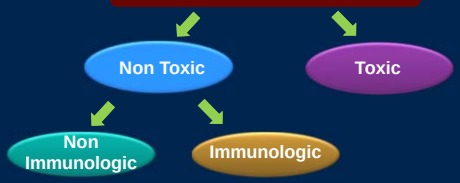
Adverse Reactions to Food

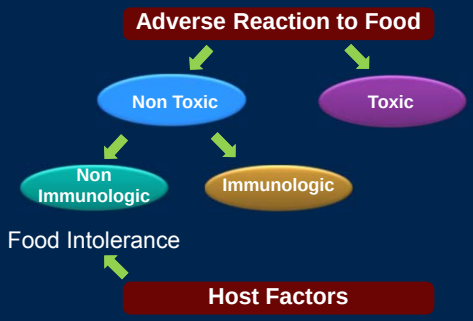


Food allergy

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

Ortolani C et al. *Best Pract Res Clin Gastroenterol* 2006; 20(3):467-83.

Adverse Reactions to Food



Ortolani C et al. *Best Pract Res Clin Gastroenterol* 2006; 20(3):467-83.

Objectives

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4) Address barriers to low FODMAP/ nutrition based interventions

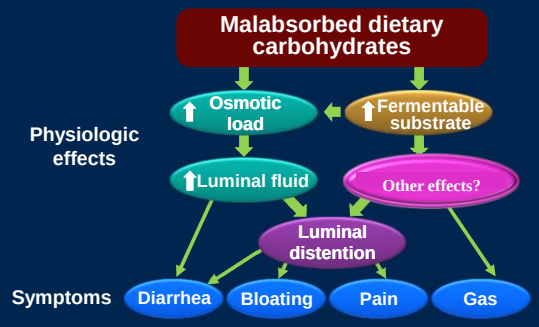
FODMAP Carbohydrates

- **F**ermentable (bacterial metabolism)
- **O**ligosaccharides (fructans/galactans)
- **D**isaccharides (lactose)
- **M**onosaccharides (fructose)
- **A**nd
- **P**olyols (sugar alcohols - sorbitol)

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

Barrett J, et al. *Pract Gastroenterol* 2007;31:51-65

FODMAP Hypothesis



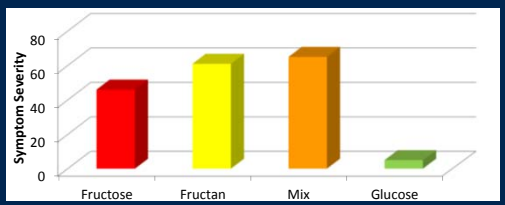
Barrett J, et al. *Pract Gastroenterol* 2007;31:51-65

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

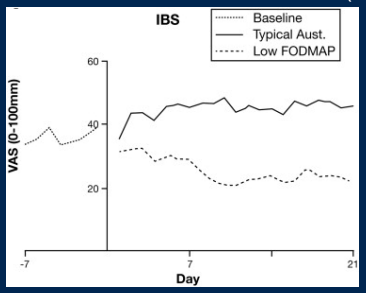
- Adult IBS – Double Blind Challenge Study



Shepherd SJ et al. *Clin Gastroenterol Hepatol* 2008;6:765-71

FODMAP Evidence Review

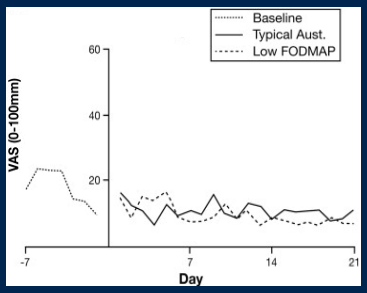
•Adult IBS – Randomized Crossover Trial (n=30)



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

FODMAP Evidence Review

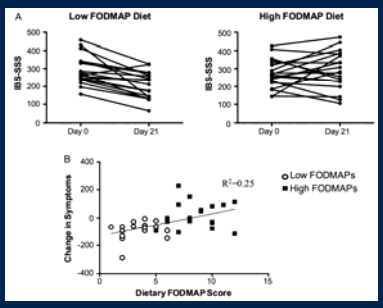
•Healthy adults – Randomized Crossover Trial (n=8)



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

FODMAP Evidence Review

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

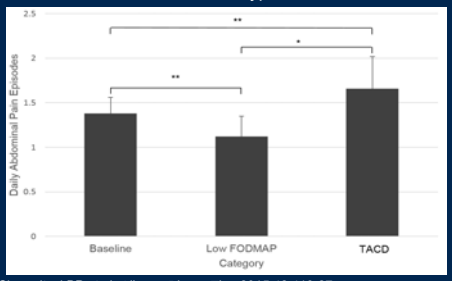


McIntosh K et al. *Gut* 2016;Mar 14 [Epub]

FODMAP Evidence Review

•Pediatric IBS – Randomized Crossover Trial (n=33)

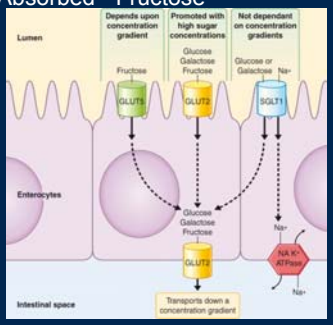
-48 hour interventions; TACD=Typical American Childhood Diet



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

FODMAP Pathogenesis

•Poorly Absorbed - Fructose



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

FODMAP Pathogenesis

•Poorly absorbed

-Lactose

•Lactase

-Fructans/Galactans

•Fructose/Galactose polymers

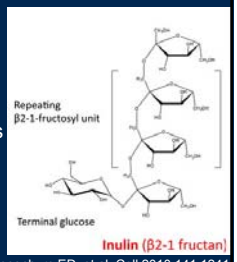
•Lack human hydrolases

•Essentially intact into colon

-Sugar alcohols

•Sorbitol, Xylitol, Mannitol

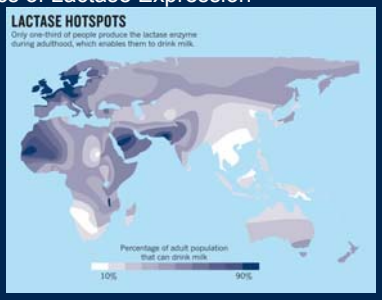
•Passive absorption



Sonnenburg ED, et al. Cell 2010;141:1241

FODMAP Pathogenesis: Genetics

•Genetics of Lactase Expression



Curry A *Nature* 2013;500:20-22

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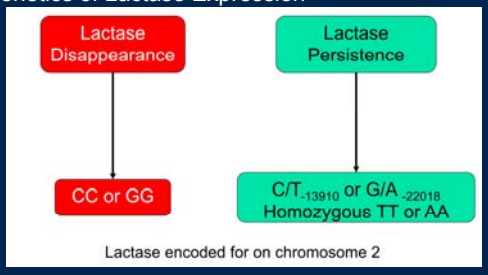


Campbell AK et al. *Sci Prog* 2009;92:241

FODMAP Pathogenesis: Genetics

•Genetics of Lactase Expression

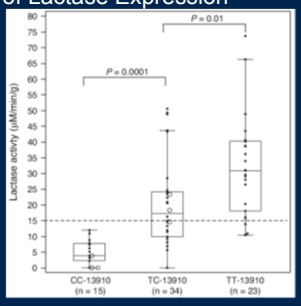
- Similar overall frequency in IBS vs. healthy controls
- May vary within IBS subtypes

Genotype	IBS-D (n=79)	IBS-C (n=52)	IBS-A (n=19)	Controls (n=252)	P value
CC	90%	46%	39%	61%	<0.001
CT	8%	48%	63%	33%	<0.001
TT	2%	6%	0	6%	-
GG	87%	42%	32%	61%	<0.001
GA	8%	46%	58%	31%	<0.001
AA	5%	12%	10%	8%	-

Kumar S et al. *J Gastroenterol Hepatol* 2012;27:1825-30.

FODMAP Pathogenesis: Genetics

•Genetics of Lactase Expression



Baffour-Awuah NY et al. *J Pediatr Gastroenterol Nutr* 2015; 60:182

FODMAP Pathogenesis: Genetics

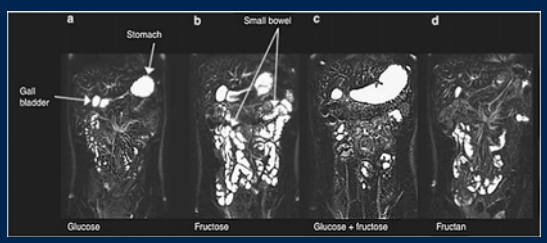
•Genetics of Sucrase-isomaltase Expression

- 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; 60:83:721-727
[2]Ringrose RE et al. *Dig Dis Sci* 1980;5:384-387
[3]Chumpitazi BP et al. *J Pediatr Gastroenterol Nutr* 2015; 61:S47-48 [abstract]

FODMAP Pathogenesis

•Osmotically active - Fructose



Murray K et al. *Am J Gastroenterol* 2014;109:110-9

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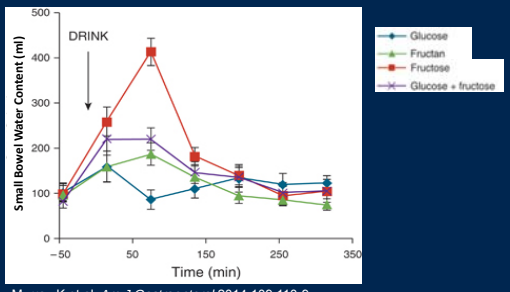


Murray K et al. *Am J Gastroenterol* 2014;109:110-9

FODMAP Pathogenesis

•Osmotically active

-Mannitol increases small bowel water content 10x versus glucose in healthy volunteers[1]

-Dietary FODMAP content correlates with ileostomy output[2]

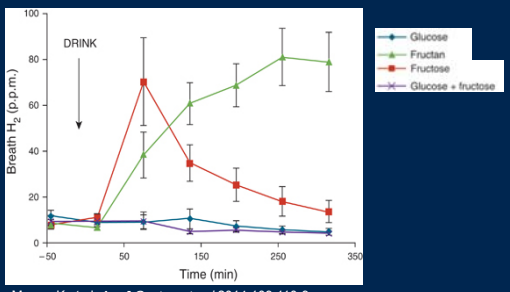
•Higher output with higher FODMAP content

-Enteral formulas with lower FODMAP content cause less enteral nutrition-associated diarrhea[3]

[1]Marciani L et al. *Gastroenterology* 2010;138:469-77
[2]Barret JS et al. *Aliment Pharmacol Ther* 2010;31:874-882
[3]Halmos EP *J Gastroenterol Hepatol* 2013;28(Suppl4):25-28

FODMAP Pathogenesis

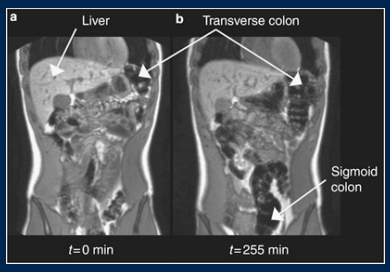
•Highly Fermentable



Murray K et al. *Am J Gastroenterol* 2014;109:110-9

FODMAP Pathogenesis

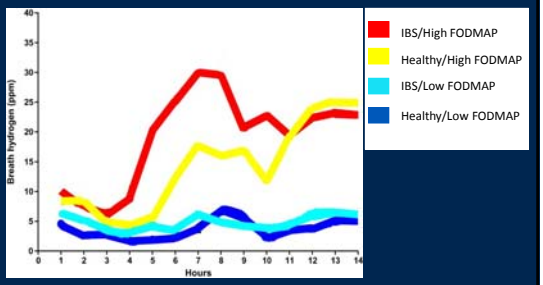
- Highly Fermentable



Murray K et al. *Am J Gastroenterol* 2014;109:110-9

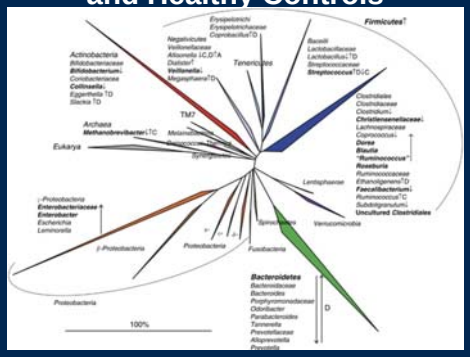
FODMAP Pathogenesis

- 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



Rajilic-Stojanovic M, et al. *Am J Gastroenterol* 2015; 110:278-287

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

[1]Staudacher HM et al. *J Nutr* 2012;142:1510-1518
[2]Halmos EP et al. *Gut* 2015;64(1):93-100
[3]Chumpitazi BP et al. *Gut Microbes* 2014;5:1-11

FODMAP Pathogenesis: Responders and Baseline Microbiome Composition

OTU	Taxonomy	LDA (Log 10)	P-value
2921213	Bacteroides (genus)	4.11	.0054
358781	Ruminococcaceae (family)	3.98	.0048
175441	Faecalibacterium prausnitzii (species)	3.53	.032
178081	Ruminococcaceae (family)	3.49	.025
4446898	Bacteroides (genus)	3.48	.042
297057	Bacteroides (genus)	3.22	.013
4417335	Bacteroides (genus)	3.14	.03
187505	Dorea (genus)	3.1	.048
171559	Bacteroides (genus)	3.06	.015
4463532	Clostridiales (order)	2.86	.023

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

Chumpitazi BP et al. *Aliment Pharmacol Ther* 2015; 42(4): 418-27

FODMAP Pathogenesis: Responders and Microbial Metabolic Potential

KO	Pathway	LDA (Log 10)	P-value
KO2529	LacI family transcriptional regulator	2.23	.028
KO1209	Alpha-N-arabinofuranosidase	2.11	.045
KO3496	Chromosome partitioning protein	2.03	.024

- 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

Chumpitazi BP et al. *Aliment Pharmacol Ther* 2015; 42(4): 418-27

FODMAP Pathogenesis: Nonresponders and Baseline Microbiome Composition

OTU	Taxonomy	LDA (Log 10)	P-value
4358723	Bacteroides (genus)	2.8	.033
347529	Turicibacter (genus)	2.65	.026
17859	Clostridialies (order)	2.6	.044
248902	Turicibacter (genus)	2.59	.015

- Uniquely enriched in *Turicibacter*
  - Fermentatative capacity for grains given to animals
  - Decreased fructo-oligosaccharide fermentation capacity
  - *T. sanguinis* with limited carbohydrate capacity
- Enriched in bacteria unable to ferment FODMAPs

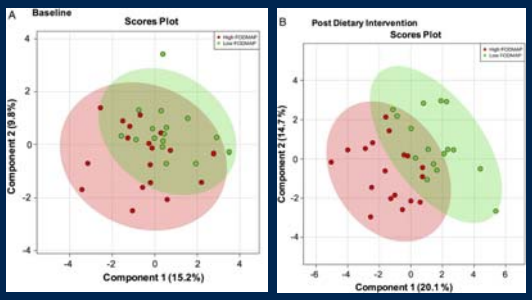
Chumpitazi BP et al. *Aliment Pharmacol Ther* 2015; 42(4): 418-27

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

Rajilic-Stojanovic M, et al. *Am J Gastroenterol* 2015; 110:278-287

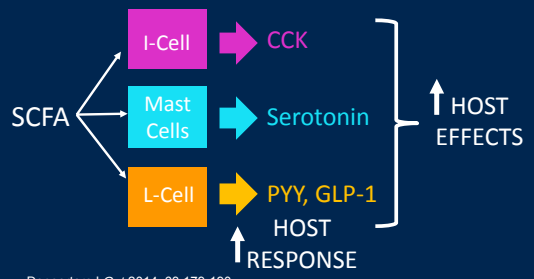
FODMAP Pathogenesis: Metabolomics



McIntosh K et al. *Gut* 2016;Mar 14 [Epub]

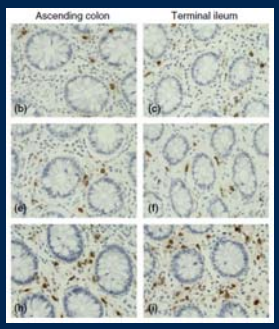
Microbiome Related Pathogenesis: Short Chain Fatty Acids

•SCFAs are a potential mechanism



Depoortere I *Gut* 2014; 63:179-190

FODMAP Pathogenesis: Inflammation



Healthy Control

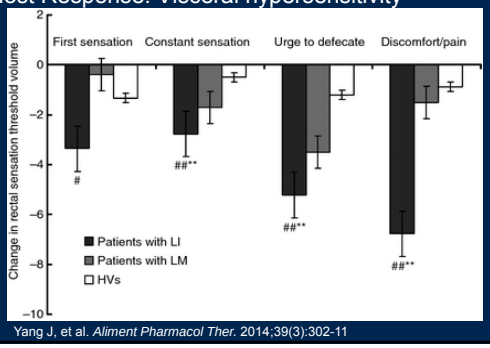
Lactose Malabsorption

Lactose Intolerance

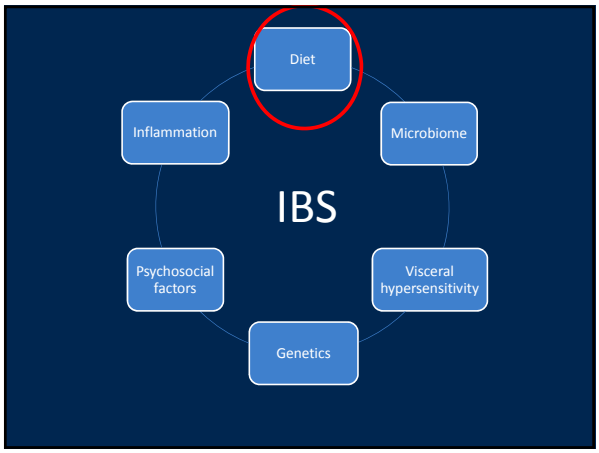
Yang J, et al. *Aliment Pharmacol Ther.* 2014;39(3):302-11

Food Intolerance Pathogenesis

•Host Response: Visceral hypersensitivity



Yang J, et al. *Aliment Pharmacol Ther.* 2014;39(3):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

Warman 2013

Low FODMAP Diet - Reintroduction

- Polyols → Lactose → Fructose → Fructans → Galactans
- Fructose → Polyols → Lactose → Fructans → Glacatans
- 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:

Carbohydrate	Amount
Polyols: Sorbitol Mannitol	 2-4 dried apricots ½ cup mushrooms
Lactose	½ - 1 cup milk
Fructose	½ mango or 1-2 tsp honey
Fructans	2 slices of wheat bread, 1 garlic clove or 1 cup pasta
Galactans	½ cup lentils or chickpeas

Low FODMAP Diet

- High FODMAP food
  - Per serving

Carbohydrate	Max Amount
Lactose	<4 grams
Mannitol/Sorbitol (Polyols)	<0.3 grams
Fructans	
Galactooligosaccharides Fructans	<0.3 grams <0.3 grams
Fructose	>0.2 grams excess of glucose

Mullin et al. JPEN 2014

Barriers

- Poor consensus
- US foods
- Full restrictions
- Partial restrictions
- Don't address food at all

Low FODMAP Diet

	Fructose	Lactose
High FODMAP	Watermelon, canned fruit, peaches, mango, pears, apples, watermelon, dried fruit, coconut milk* Asparagus, artichokes, sugar snap peas Honey, agave, high-fructose corn syrup	Milk (cow, goat, sheep), yogurt, ice cream, evaporated milk, powdered milk, soft & fresh cheeses (i.e. mascarpone, ricotta, cottage)
Substitute FODMAP	Ripe fruits: Bananas, grapefruit, honeydew, citrus fruits, strawberries, blueberries, kiwi, raspberries Male syrup, golden syrup	Lactose free milk products, unsweetened almond*/rice milk, hard cheeses (i.e. parmesan, cheddar, mozzarella, Swiss), Lactose free yogurt, butter, gelato, sorbet

- Limit 1 serving FODMAP friendly fruit per meal
- Consume ripe fruits
- *Inconclusive

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

Low FODMAP Diet

	Oligosaccharides		Polyols
	Fructans	Galactans	
High FODMAP	Watermelon Brussels sprouts, artichokes, leek, onion, beetroot, cabbage, garlic, okra, shallots, snow peas Grains such as wheat & rye Inulin & FOS	Lentils, chickpeas, legumes (beans such as: kidney, soy, baked beans) Broccoli	Stone fruits (cherries, peaches, plums), apples, pears, watermelon, blackberries Cauliflower, snow peas, mushrooms Sorbitol, mannitol, xylitol, maltitol
Substitute FODMAP	Carrots, celery, bok choy, bamboo shoots, eggplant, corn, green beans, lettuce, chives, parsnip, pumpkin, tomato, red/yellow/orange bell pepper, potatoes, spinach, butter lettuce, bean sprouts Garlic infused oil Gluten-free breads, cereals, rice, rice & corn pasta, rice cakes, plain potato chips, tortilla chips		Bananas, blueberries, grapefruit, kiwi, citrus fruits, raspberries, grapes Sugar, glucose, aspartame, sweetener w/o -'ol'

Low FODMAP Diet

Proteins	Grains	Dairy	Fruit	Vegetables
Beef, chicken, fish, egg, pork, tofu Almonds, flax, peanuts, pecans, pumpkin seeds, sunflower seeds, walnuts, nut butters (natural)	Rice, oats, quinoa, polenta, corn, rice cakes, rice crackers, oatmeal (plain), plain potato chips, tortilla chips, millet, buckwheat Gluten Free pasta, breads & flours	Lactose free dairy products, unsweetened rice/almond milk*, 1 oz hard cheese (cheddar, Swiss, feta, mozzarella) 1 Tbsp cream cheese	Banana, blueberries, cantaloupe, grapefruit, grapes, honeydew, citrus fruits, raspberries, rhubarb, strawberries, kumquat, tangelo	Zucchini, squash, tomato, turnip, spinach, potato, parsnip, olives, lettuce, eggplant, cucumber, chives, carrots, celery, Brussels sprouts, bok choy, green beans, bamboo shoots, sprouts

Note: portion size is important and some of the vegetables require limited intake as they are moderate in FODMAP concentration

Focus on the FODMAP Friendly Snacks

- •Vegetables
- •Rice cakes
- •Red meat
- •Eggs
- •Hard cheeses
- •Popcorn
- •Yogurt
- •Nuts/Seeds (1-2 Tbsp)
- •Tortilla Chips
- •Gluten free pretzels/crackers
- •Natural nut butters
- •Plain kefir

Focus on 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
   - •Biesiekierski JR et al. *J Hum Nutr Diet* 2011; 24:154-176

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

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  - 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:

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

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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

COMPLEMENTARY FOODS

Infant formula
Solid foods

BREAST MILK

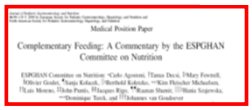
SOLID FOODS

MILK

Breast milk or infant formula

WHO

World Health Organization


Medical Position Paper

Complementary Feeding: A Commentary by the ESPGHAN Committee on Nutrition

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

Clayton HB, et al. Pediatrics. April 2013

Current Practices Introduction of CF in 5 EU Countries

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

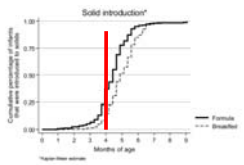


FIGURE 1. Cumulative percentage of formula-fed and breast-fed children with introduction of solids, per month.

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

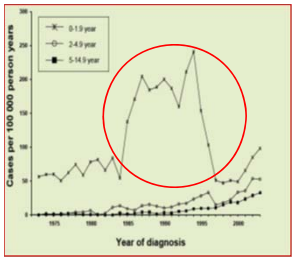
- No solid food 69.6%
- 1-2 groups 17.3%
- 3-8 groups 13.1%

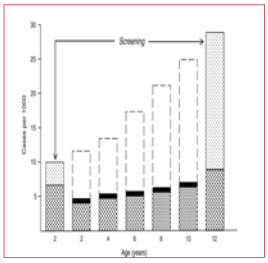
Zutavern A et al. Pediatrics 2008;121:e44-52

Complementary feeding
Previous recommendations

	Solid foods	Cow's milk	Eggs	Peanuts	Fish
AAP 2000	>4 mo	>12 mo	>24 mo	>36 mo	>36 mo
ASCIA 2006	>4-6 mo			Option	Option
ACAAI 2006		>12 mo	>24 mo	>36 mo	>36 mo

Complementary feeding and Celiac Disease

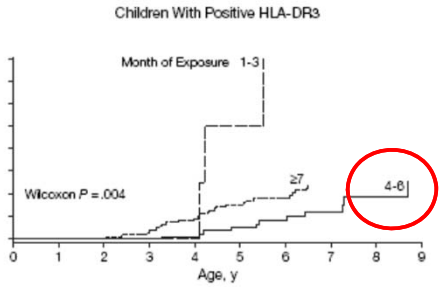




Ivarsson A et al., Acta Pædiatr 2000
Myleus A, et al. ESPGHAN 2007

JPGN 2009; 49:170-176

Age at introduction



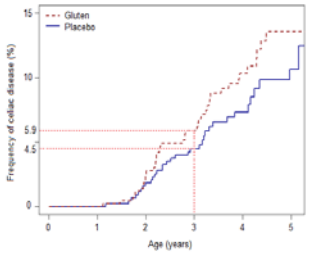
Norris JM et al., JAMA 2005

PreventCD Project

Hypothesis:
Childhood celiac disease may be prevented

By introduction of gluten

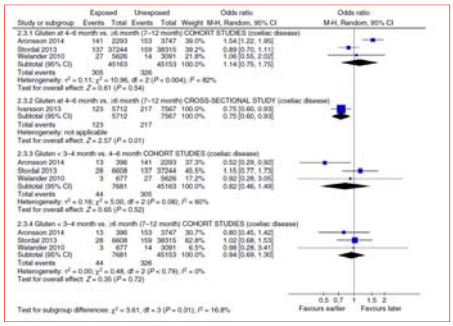
- in small amounts
- 4-6 months of age
- preferably while being breastfed



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 - 24weeks.

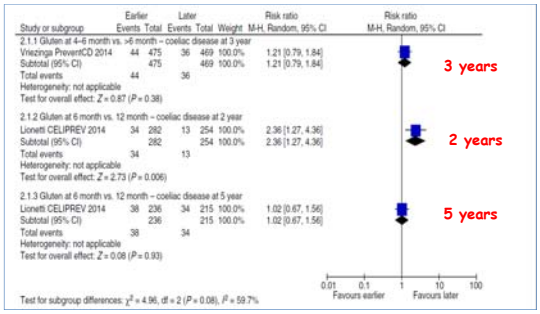
Vriezinga, et al. N Engl J Med 2014

Timing of Gluten introduction
Observational studies



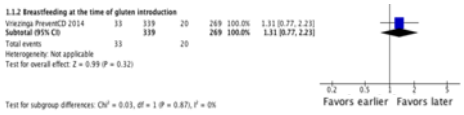
Szajewska H and Shamir R. APT 2015

Timing of Gluten introduction
RCT's



Szajewska H and Shamir R. APT 2015

Breast Feeding at Gluten Introduction
Interventional trials



Szajewska H and Shamir R. APT 2015

ESPG[illegible]ations

"……av[illegible]elow 4 month[illegible] more mo[illegible] of glute[illegible]luten wh[illegible]still breast-fed"

ESPGHAN CoN. JPGN 2009

ESPGHAN Recommendations 2016

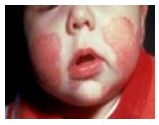
"Gluten can be introduced into the infant's diet between the ages of 4 and 12 completed months.* Age of gluten introduction..in this age range does not seem to influence the absolute risk of developing CDA or CD during childhood"
(conditional recommendation; depending on the age, quality of evidence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

*4 completed months = 17 weeks of age.

ESPGHAN. JPGN 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

Complementary feeding
Previous recommendations

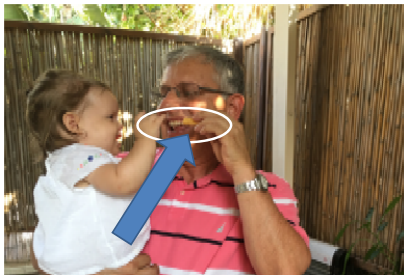
	Solid foods	Cow's milk	Eggs	Peanuts	Fish
AAP 2000	>4 mo	>12 mo	>24 mo	>36 mo	>36 mo
ASCIA 2006	>4-6 mo			Option	Option
ACAAI 2006		>12 mo	>24 mo	>36 mo	>36 mo

Complementary Feeding & Allergy

Table 1. Prospective birth cohorts evaluating the effect of the introduction of solids on the development of allergic diseases

Study	Number of children	Country	Evidence
GINI study [11]	4,753	Germany	No evidence that delayed introduction of solids beyond 4 months or delayed introduction of most allergenic foods beyond 6 months prevents the development of eczema
Lisa study [3]	2,073	Germany	No evidence that delayed introduction of solids beyond 4 or 6 months prevents allergies at the age of 6 years; for eczema, a protective effect of delayed introduction could not be excluded
KOALA study [12]	2,558	The Netherlands	Delayed introduction of cow's milk products was associated with higher risk for eczema; delayed introduction of other foods was associated with an increased risk for atopy at 2 years of age
Generation R study [13]	6,905	The Netherlands	No evidence for eczema and wheezing prevention of delayed introduction of allergenic foods after 6 months of age

Shamir R. The Nest 2013

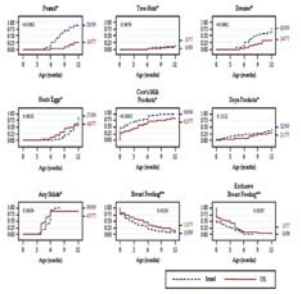


Early consumption of peanuts in infancy and peanut allergy

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<0.0001)

The prevalence of PA in the UK **was 1.85%**, and the prevalence in Israel was **0.17%** (P < .001).



Du Toit G. J Allergy Clin Immunol 2008

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

A. Lindsay Frazier, MD, ScM; Carlos A. Camargo Jr, MD, DrPH; Susan Malspeis, MS; Walter C. Willett, MD, DrPH; Michael C. Young, MD

JAMA Pediatrics 2014

Model[a]	Maternal Peripregnancy P/TN Consumption					
	<1 Serving/mo	1-3 Servings/mo	1-4 Servings/wk	≥5 Servings/wk	P_{trend}[b]	$P_{interaction}$[c]
All mothers						
Child P/TN allergy, No./Total No.	60/2747	23/1201	40/2891	17/1366		
OR (95% CI)						
Unadjusted	1 [Reference]	0.87 (0.54-1.42)	0.63 (0.42-0.94)	0.56 (0.33-0.97)	.03	.009
Multivariable[d]	1 [Reference]	0.90 (0.55-1.48)	0.65 (0.43-0.97)	0.58 (0.34-0.99)	.04	.002
Mothers without P/TN allergy						
Child P/TN allergy, No./Total No.	39/2692	15/1179	22/2844	6/1344		
OR (95% CI)						
Unadjusted	1 [Reference]	0.88 (0.48-1.60)	0.53 (0.31-0.90)	0.31 (0.13-0.72)	.003	
Multivariable[d]	1 [Reference]	0.94 (0.51-1.74)	0.56 (0.33-0.95)	0.31 (0.13-0.75)	.004	
Mothers with P/TN allergy						
Child P/TN allergy, No./Total No.	21/55	8/22	18/47	11/22		
OR (95% CI)						
Unadjusted	1 [Reference]	0.93 (0.32-2.67)	1.00 (0.45-2.25)	1.62 (0.55-4.75)	.31	
Multivariable[d]	1 [Reference]	1.28 (0.39-4.17)	1.03 (0.42-2.56)	2.62 (0.74-9.27)	.12	

The LEAP Study

Leap
Learning Early About Peanut Allergy

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

Negative

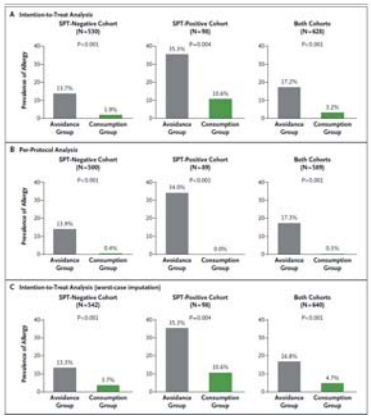
2 g of peanut protein in a single dose and excluded if reacted

Positive test 1-4 mm

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

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

Du Toit, et al. N Engl J Med 2015



Du Toit, et al. N Engl J Med 2015

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."

Du Toit, et al. N Engl J Med 2015

- "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?"

Editorial. N Engl J Med 2015

- Are there lessons to be learned from celiac disease?

The EAT Study

EAT
Enquiring About Tolerance

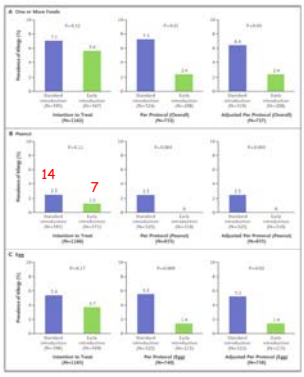
❖ Recruited, from the general population, 1303 exclusively BF infants, 3 months.

❖ 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).

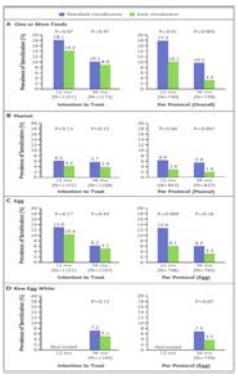
❖ Primary outcome: food allergy to one or more of the six foods between 1 year and 3 years of age.

Perkin et al. N Engl J Med 2016

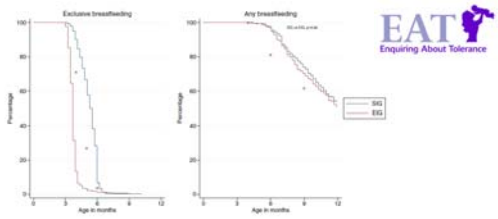
Primary Outcome of Allergy to One or More Foods and Secondary Outcomes of Allergy to Peanut and to Egg



Secondary Outcome of Results on Skin-Prick Testing



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



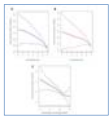
EAT
Enquiring About Tolerance

Perkin et al. JACI 2016

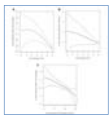
Food, drug, insect sting allergy, and anaphylaxis

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

Caroline Roduit, MD, MPH,[a] Remo Frei, PhD,[b] Martin Depner, PhD,[c] Bianca Schaub, MD,[c] Georg Loss, PhD,[d] Jon Genuneit, MD,[e] Petra Pfefferle, PhD,[f] Anne Hyvarinen, PhD,[g] Anne M. Karvonen, PhD,[g] Josef Riedler, MD,[h] Jean-Charles Dalphin, MD, PhD,[i] Juha Pekkanen, MD,[g] Erika von Mutius, MD, MSc,[c] Charlotte Braun-Fahrländer, MD,[d,k] Roger Lauener, MD,[l] and the PASTURE study group*
Zurich, Basel, and Davos, Switzerland, Munich, Ulm, and Marburg, Germany, Kuopio, Finland, Schwarzach, Austria, and Besançon, France



Asthma



Food Allergy

- 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

JACI 2014;133:1056-64

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

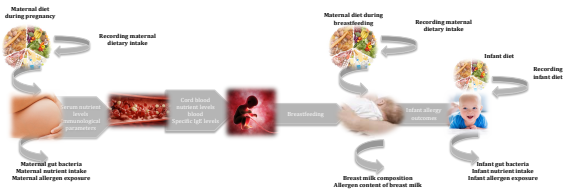
I have the following financial relationships to disclose:

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

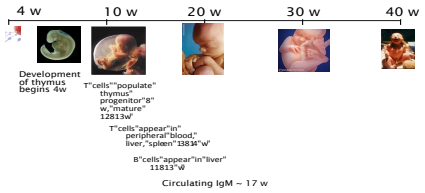


The MOST important take-away points

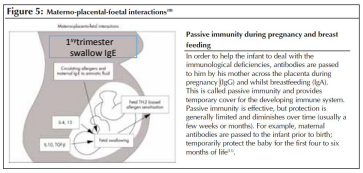
- Prevention **DOES NOT EQUAL** management
  - It is two different worlds!
  - Like moving from the Isle of Wight to Cincinnati

Pregnancy

Development of the Human Immune System



Immune system during pregnancy



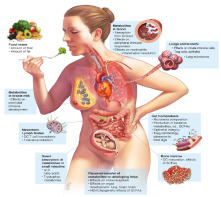
Vance et al. Pediatr Allergy Immunol 2002: 13 (Suppl. 15): 14–18
Vance et al. Clin Exp Allergy 2004; 34:1855–1861
Pastor-Vargas et al. Pediatr Allergy Immunol 2016 *In press*

PEDIATRIC ALLERGY AND IMMUNOLOGY

Factors associated with maternal dietary intake, feeding and weaning practices, and the development of food hypersensitivity in the infant

The picture is so much bigger than this!

Venter et al. *J Hum Nutr Diet.* 2006;19(2):129-38



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

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

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

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

http://www.who.int/nutrition/publications/optimal_duration_of_exc_bfeeding_report_eng.pdf

Breast Milk

Immune-regulating substances

- Immunoglobulin A
- Oligosaccharides
- Long chain fatty acids …
- Cytokines
- Nucleotides
- Hormones
- Antioxidants
- Maternal immune cells
- Lactoferrin
- Lysozymes
- Dietary antigens
- Carotene 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 lactaon, 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
Verhasselt et al. Curr Opin Immunol. 010;22:623 0.
Lipkie et al. PLoS One. 2015;10:e0127729.
Ballard and Morrow Pediatr Clin orth Am. 2013;60:49-74.

Cincinnati Children's

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…

Lovegrove et al. Gut. 1993;34:203-7.
Hattevig et al. Clin Exp Allergy. 1989;19:27-32.
Palmer et al. Clin Exp Allergy. 2008 Jul;38(7):1186-91.

Cincinnati Children's

Breast Feeding

- Exclusive breast-feeding is recommended for at least 4 months and up to 6 months of age to:
  - Possibly reduce the incidence of atopic dermatitis for children <age 2 years
  - Reduce early onset wheezing <age 4 years
  - Reduce the incidence of cow's milk allergy (CMA) but not food allergy in general in the first 2 years of life
- The effects of breastfeeding on allergic rhinitis are not clear at this time.
- There is no need to avoid allergens during breast feeding

Maternal diet factor	During lactation
Prebiotics	No recommendations due to insufficient evidence
Probiotics	Use recommended for reduced atopic dermatitis/ eczema outcomes
Vitamin D	No recommendation at present
Omega-3 long chain fatty acids	No recommendation
Food allergen elimination/ alteration	Not recommended due to insufficient evidence
Healthy diet	No current studies

Fleischer et al. JACI IP 2013;1:29-36
Palmer, Brown, Maslin and Venter Invited review Pediatr Allergy Immunol 2016

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When things go wrong..

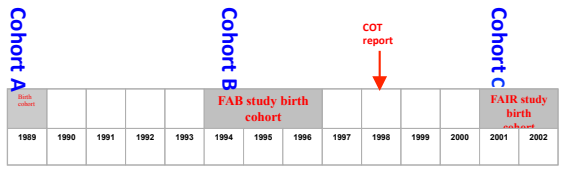
COT (UK) report on peanut allergy (1998)

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.

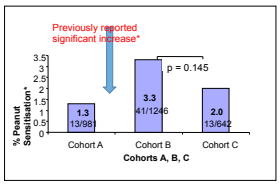
Now withdrawn

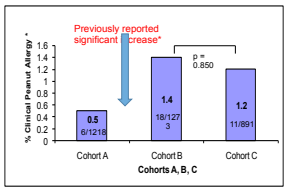
hps: //cot.food.gov.uk/committee/committee-on-toxicity/cotreports/cotwgreports/cotpeanutallergy

Isle of Wight: Peanut allergy



Changes in sensitisation/clinical allergy to peanut





Venter et al. *Allergy*. 010;65:103 .

Cincinnati Children's

The overlap…

Cincinnati Children's

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

Poole et al. Pediatrics 2006;117:2175-82.

Cincinnati Children's

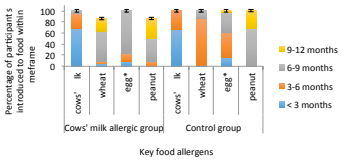
PIFA data from Southampton

- 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

Grimshaw et al. Pediatrics. 2013;132:e1529-38.
Grimshaw et al. Clin Transl llergy. 2016; 26;6:1.
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

Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis

Robert J Boyle,[1 2] Despo Ierodiakonou,[1 2] Tasnia Khan,[1] Jennifer Chivinge,[2] Zoe Robinson,[2] Natalie Geoghegan,[2] Katharine Jarrold,[2] Thalia Khaitiou,[2] Tim Reeves,[2] Sergio Cunha,[3] Marialena Trivella,[4] Vanessa Garcia-Larsen,[5] Jo Leonardi-Bee[6]

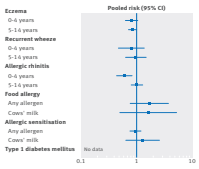


Fig 2 | Summary of treatment effects of hydrolysed formula on different outcome measures. Data shown are mean risk ratios (for allergic rhinitis at age 0-4; food allergy; allergic sensitisation; diabetes) or odds ratios (all other outcomes) with 95% confidence intervals for partially hydrolysed formula compared with standard cow's milk formula

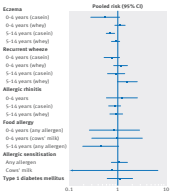


Fig 3 | Summary of treatment effects of hydrolysed formula on different outcome measures. Data shown are mean risk ratios (for allergic rhinitis at age 0-4; food allergy; allergic sensitisation; diabetes) or odds ratios (all other outcomes) with 95% confidence intervals for extensively hydrolysed formula compared with standard cows' milk formula

Cincinnati Children's changing the outcome together

WHAT IS ALREADY KNOWN ON THIS TOPIC

Breastfeeding is the optimum mode of nutrition for infants

Substitution with infant formula has been associated with allergic and autoimmune disease

International guidelines recommend use of a hydrolysed formula in place of standard infant formula for infants at risk of allergic disease to prevent eczema and allergy to cows' milk

WHAT THIS STUDY ADDS

There is no consistent evidence to support the use of hydrolysed formula for the prevention of allergic or autoimmune disease

the bmj | *BMJ* 2016;352:i974 | doi: 10.1136/bmj.i974

Cincinnati Children's changing the outcome together

Early life feeding

Cincinnati Children's changing the outcome together

Healthy Eating and Solid Food Intake…

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

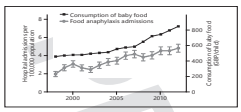


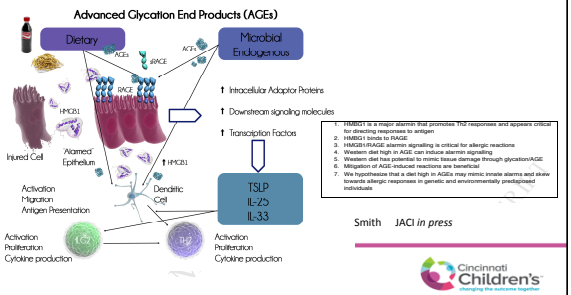
Fig. 1. Sales of commercial baby food in the UK versus admissions in food-related anaphylaxis (adapted from ref. 31).

Clinical 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.

Grimshaw . J Allergy Clin Immunol. 2014;133:511-9.

Cincinnati Children's

Commercial foods



1. HMBG1 is a major alarmin that promotes Th2 responses and appears critical for directing responses to antigen
2. HMBG1 binds to RAGE
3. HMGB1-RAGE alarmin signalling is critical for allergic reactions
4. Western diet high in AGE can induce alarmin signalling
5. Western diet has potential to mimic tissue damage through glycation/AGE
6. Mitigation of AGE-induced reactions are beneficial
7. We hypothesize that a diet high in AGEs may mimic innate alarms and skew towards allergic responses in genetic and environmentally predisposed individuals

Smith JACI *in press*

Cincinnati Children's

Role of Food Diversity

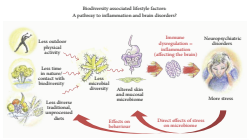
- Finnish study: n= 3142 infants
- By 3 to 4 months of age, food diversity was not associated with any of the allergic end points
- By 6 months of age, less food diversity was associated with increased risk of allergic rhinitis but not with the other end points
- **By 12 months of age, less food diversity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

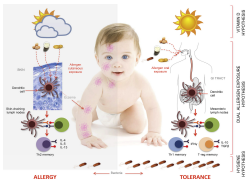
Nwaru et al. J Allergy Clin Immunol. 2014;133:1084-91

Cincinnati INDANA
International Network for Diet and Nutrition in Allergy

Isle of Wight – Diet Diversity

- In participants with eczema at 9 months (OR 0.804, 95% CI 0.65-0.98, p = 0.035) or 12 months (OR 0.658 95% CI 0.40-1.07, p = 0.091), 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.

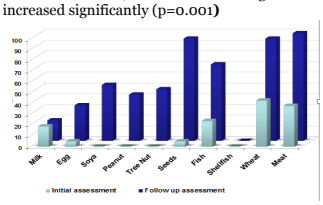




Prescott et al. International Journal of Biodiversity Volume 2016, Article ID 2718275
Du Toit J Allergy Clin Immunol. 016 Jun 8. pii: S0091-6749(16)30262-7.
Venter and Maslin submie d for publicaon

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=0.001)



BSACI poster presentation Tarkin M et al. 2013

What did LEAP and EAT teach us?

NAIAD guidelines open for comment

SPT	0-2 mm	3-7 mmm	8 mm and above
First feed	Give one dose at home/ hospital	Give graded challenge in hospital (3.9 g protein)	Accept allergic…
Continued intake at home	2 g peanut protein, 3 x per eek	2 g peanut protein, 3 x per eek	avoid

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

Peanut butter TOTAL amount of protein = 3.96 g

Teaspoon	g (peanut butter)	g (peanut protein)
¼	0.67	0.15
½	1.33	0.29
½	2.67	0.59
1	5.33	1.17
1 ½	8	1.76

Peanut flour TOTAL = amount of protein 3.88 g

Teaspoon	g (peanut flour)	g (peanut protein)
¼	0.25	0.13
¼	0.5	0.25
½	1	0.5
1	2	1
2	4	2

Peanut powder TOTAL = amount of protein 3.88 g

Teaspoon	g (peanut powder)	g (peanut protein)
¼	0.25	0.13
¼	0.5	0.25
½	1	0.5
1	2	1
2	4	2

Bamba TOTAL = amount of protein 3.9 g

# Sticks	g (Bamba)	g (peanut protein)
1	0.81	0.1
3	2.43	0.3
5	4.05	0.5
10	8.1	1
21	17.01	2

What does 2 g of peanut look like?

	Bamba	Peanut butter	Peanuts	Peanut flour/ powder	Peanut butter containing cereals	Reese's cups
Amount containing approximately 2 grams peanut protein	17 or 2/3 of a 28 g (1oz) bag or 21 'sticks'	9-10 g or 2 teaspoons	8 g or ~10 whole peanuts	4 g or 2 teaspoons	¾ - 2 cups depending on brand	1 large cups

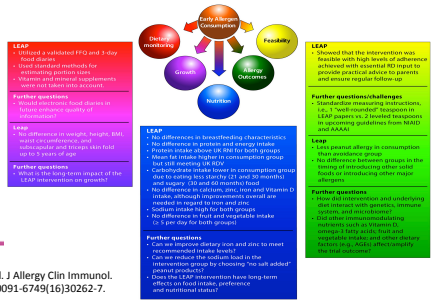
Cincinnati Children's

Nutritional Composition of Peanut Butter Alternatives

Per approx. 2 g Peanut protein:	Bamba (17 g)	Peanut butter (10 g)	Peanuts (8 g)	Peanut flour (4 g)	Cereal (50 g)	Cereal (140 g)	Reese's (21 g - 1 cup)
Kcals	91	59	45	13	210	550	105
Sugar (g)	0.6	0.65	0.38	0.33	13	45	10.5
Salt (mg)	70	48	1	7	225	649	75
Fat (g)	6.0	4.95	3.94	0.02	4.8	7.5	6.5

Cincinnati Children's

LEAP nutrition paper



Feeney et al. J Allergy Clin Immunol. 2016. ii: 0091-6749(16)30262-7.

nnati ildren's

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 3 egg white protein/egg i.e. **6 g**)
  - Fish: 25 grams fish (**5.1 g**)
  - Peanuts: 3 teaspoons of peanut butter (**3 g**)

N Engl J Med. 2016;374(18):1733-43.

Cincinnati Children's

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

Cincinnati Children's

Thank you!

Cincinnati Children's