Clinical Science: Year in Review 2015

What’s Hot?
William F. Balistreri, M.D.

Goal: Uncover….

“What’s Trending”
Articles published since we met last October

Disclaimer

Lay
Press
They digest only 17% of the 50-100 pounds of bamboo they eat each day!

Bam-boo ➔ Bam-poo
Both herbivores, pandas. The evolution of the gut microbiota in the giant and the red panda.
Both herbivores have evolved anatomically specialized guts to efficiently deconstruct fibrous plant matter, NOT the panda - “they lack cellulose-digesting enzymes”
The good news...

They have adapted

**ANIMAL PHYSIOLOGY**


**Exceptionally low daily energy expenditure in the bamboo-eating giant panda**

Yonggang Nie,1–4 John R. Speakman,2,3 Qi Wu,3,4 Chenglin Zhang,3 Yihe Hu,3 Minhua Xia,4 Li Yan,1 Catherine Hamblé,5 Lu Wang,7 Wei Wei,1 Jingna Zhang,8 Foswin Wu1

The common giant panda has a specialized bamboo diet, to which its alimentary tract is poorly adapted. Measurements of daily energy expenditure across the captive and three wild pandas averaged 5.2 megajoules (MJ/day; only 37% of the predicted value (13.8 MJ/day). For the wild pandas, the mean was 6.2 MJ/day, or 45% of the mammalian expectation. Pandas achieve this exceptionally low expenditure in part by reduced sizes of several subcubular organs and low physical activity. In addition, circulating levels of thyroid hormones thyroxine (T4) and triiodothyronine (T3) averaged 46.3 and 64%, respectively, of the levels expected for a eutherian mammal of comparable size. A giant panda–unique mutation in the *DUOX2* gene, critical for thyroid hormone synthesis, might explain these low thyroid hormone levels. A combination of morphological, behavioral, physiological, and genetic adaptations, leading to low energy expenditure, likely enables giant pandas to survive on a bamboo diet.
**Animal Physiology**

**Nie, Science 349:171, 2015**

**Exceptionally low daily energy expenditure in the bamboo-eating giant panda**

They achieve this by:
- reduced size of liver, brain, etc.
- low physical activity
- low levels of thyroid hormones

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Surface Temperatures (°C)

Surface Temperature (°C)

"Pandas live life in a metabolic slow zone"
However, they do more than eat, poop, sleep:

If you walk through the exhibit there will be piles of panda poop...

National Zoo’s giant panda Mei Xiang gives birth to two cubs hours apart

Giant Pandas at the Smithsonian’s National Zoo

"If you walk through the exhibit there will be piles of panda poop..."
Infection’s Link to Functional GI Disorders

Pensabene, J Pediatrics 166:903, 2015

Postinfectious Functional Gastrointestinal Disorders in Children: A Multicenter Prospective Study

Lisa Pensabene, MD, PhD,1 Valentina Toscano, MD,1 Donatella Cinotti, MD,1 Domenico Clibera, MD,1 Angelica Cusumano, MD,1 Elena Barba, MD,1 Anna cucinelli, MD,2 Angelo Guglielmi, MD,1 Teresa Carita, MD,1 Veronica Righi, MD,1 Silvio Saraceno, MD,1 Annarosa Stabile, MD,1 and Carlo G Iannetta, MD,1 on behalf of the Post-infectious Functional Gastrointestinal Disorders Study Group of the Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition

Objective To prospectively investigate the occurrence of postinfectious functional gastrointestinal disorders (FSGID) diagnosed according to the Rome III criteria, in children with acute diarrhea of different infections.

Study design This was a prospective cohort interviewer study. Children 0.1-14 years of age presenting with acute diarrhea were enrolled in the study from May 2010 to December 2012.

Results A total of 1775 patients (653 boys, median age 4.3 years; range 0.1-14.1 years) were recruited. 32 subjects had a diagnosis of FSGID, 12 in the control and 20 in the case group. There were no differences in age, sex, or number of stool episodes between the subjects with and without FSGID. The most common FSGID were abdominal pain (33%), nausea (20%), anorexia (10%), and vomiting (3%).

Conclusion: This prospective cohort multicenter study supports postinfectious FSGID as a true entity in children. There seems to be a significant increase in abdominal pain-related FSGID after acute diarrhea in children within 1 month and 3-6 months later. J Pediatr 2015;168:903-9.
Increase in abd pain–related FGIDs after acute diarrhea

Etiology of acute diarrhea in children with FGIDs at 6 months

Pensabene, J Pediatrics 166:903, 2015

Postinfectious Functional Gastrointestinal Disorders in Children: A Multicenter Prospective Study

Licia Pensabene, MD, PhD, Vincenzo Troiano, MD, Domenico Cistala, MD, Gennaro Ciliberto, MD, Angela Cappuccio, MD, Teresa Gamba, MD, Vincenzo Ruggeri, MD, Silvia Sansone, MD, Antonino Stanco, MD, and Carlo Di Lorenzo, MD, on behalf of the Post Infectious Functional Gastrointestinal Disorders Study Group of the Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition

Objectives To prospectively investigate the occurrence of postinfectious functional gastrointestinal disorders (FGIDs) diagnosed according to the Rome III criteria, in children with acute diarrhea of different infectious etiologies.

Study design This was a prospective cohort multicenter study. Children 4-11 years of age presenting with acute diarrhea of different infectious etiologies were enrolled at the time of the acute episode and monitored with control subjects of similar age and sex. Symptoms were evaluated with an updated questionnaire for FGIDs at the time of enrollment in the study and after 1, 3, and 6 months.

Results A total of 61 patients (36 boys; median age 6.3 years; age range 4.1-14.1 years) were recruited. 32 subjects in the acute phase were infected with rotavirus (18.3%), adenovirus (11.5%), norovirus (9.9%), and Giardia lamblia (3.7%). FGIDs were significantly more common in exposed patients compared with controls within 1 month from acute diarrhea (P = 0.0019, RR = 2.24), and 6 months after acute diarrhea (P < 0.01, RR = 1.98) alone. No correlation was found between different etiologies, age, sex, and severity of FGIDs. Among exposed children, abdominal pain–related FGIDs were significantly more frequent compared with controls after 6 months from infection (P = 0.044, RR = 1.72).

Conclusions This prospective cohort multicenter study supports postinfectious FGIDs as a true entity in children. There seems to be a significant increase in abdominal pain–related FGIDs after acute diarrhea in children within 1 month and 3 and 6 months later. J Pediatr. 2015;166:903-9
1811 children-foodborne Salmonella F/U 16 years later:
• 37% IBS (23% controls)
• odds ratio for IBS in exposed = 1.9
The New York Times

The Opinion Pages | EDITORIAL

September 4, 2015

Cheeseburger, Hold the Salmonella

By THE EDITORIAL BOARD  SEP. 4, 2015

In a lot of beef. It’s also a lot of chicken, and it can harbor dangerous bacteria. At least 700 people were sickened and four children died after eating tainted hamburgers. But as a new report points out, there is more the Department of Agriculture and the Food and Drug Administration can do to keep Americans safe and some simple things consumers could do themselves.

...not just IBS!

The Washington Post

Local

70 possible cases of salmonella linked to Fig & Olive in the District

September 26, 2015

NASPghan ★★★ 2015

Annual Meeting & Postgraduate Course

“Naspys”

Potential Advocacy Issue of the Year

October 7-11, 2015 • Washington Hilton • Washington, DC
Potential Advocacy Issue of the Year
Food Safety (?) System

October 7–11, 2015 • Washington Hilton • Washington, DC

The State of Food Safety in the U.S.

Two recent CDC reports examine the state of food safety in the United States. One measures foodborne illnesses and the other summarizes foodborne outbreaks. Overall, the results from both reports show that progress has been made but more work is needed.

Annual Food Safety Progress Report
The annual food safety progress report measures foodborne illnesses from nine key genres and is produced from 2014 data compiled by the Foodborne Diseases Active Surveillance Network (FoodNet). This year’s report showed some progress in reducing infections from E. coli O157 and one type of Salmonella, however, there’s still work to be done. Illness from six other enteric bacteria monitored by FoodNet increased.

- 48 million cases of food-borne diseases
- 3,000 deaths/year

The New York Times
September 5, 2015

Cucumbers Recalled in Salmonella Outbreak

The Centers for Disease Control and Prevention said cucumbers from Mexico were linked to the largest outbreak of salmonella to date...
October 6, 2015

4 dead. 732 sickened in cucumber salmonella outbreak. Toll keeps going up.

National outbreak (2009):
-714 cases in 46 states
-9 deaths

How Safe Is Your Ground Beef?
Fecal contamination in all 458 pounds of beef examined

Staphylococcus aureus
Clostridium perfringens
Salmonella species
Escherichia coli
Enterococcus species

More...
BAD NEWS!
Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study
Collier, Lancet Infect Dis. 14:976, 2014

Summary
Background In May 2013, an outbreak of symptomatic hepatitis A shore infections occurred in the USA. Federal, state, and local public health officials investigated the cause of the outbreak and assessed the public health implications.

Methods We interviewed patients, obtained their shopping information, reviewed patient surveys, and sampled products. We tested products.

Findings Of 163 patients identified from ten states, 63 (39%) were admitted to hospital and one needed a liver transplant; three died. Illness started between June 2 and August 13. Overall, 104 patients (64%) had food in their freezer, and 119 had Hepatitis A virus genotype IIIB. Among the patients, two were hepatitis A virus carriers. Pomegranate arils that were imported from Turkey were found to contain B. subtilis spp. subtilis.
Whole Foods Recalls Papillon Organic Roquefort Cheese Due to Listeria Risk  
October 8, 2015

Whole Foods Market is recalling Papillon Organic Roquefort cheese sold in all of its stores nationwide that came from its supplier because it has the potential to be contaminated with Listeria monocytogenes.

The recalled cheese was cut and packaged in clear plastic wrap and sold with Whole Foods Market sale labels. Whole Foods decided to recall the cheese after routine sampling conducted by the U.S. Food and Drug Administration found Listeria monocytogenes in a small amount of the cheese.

The Papillon Organic Roquefort cheese product can be identified by the scale label that begins with 128 and 052. All sell-by dates are affected.

No illnesses or hospitalizations have been reported to date. Signage is posted on all store shelves to notify customers of the recall, and all affected product has been removed from shelves.

New FDA Rules Tighten Food Safety Requirements

Manufacturers will have to devise plans to prevent foodborne illness

Ready For Some Good News?

Domestic Imported

Food Safety Modernization Act: Putting the Focus on Prevention

By Margaret A. Hamburg, M.D., Commissioner of Food and Drugs

Featured Announcements

September 10, 2015

Long-awaited rules will require food manufacturers… identify & prevent contamination in production facilities
Bottom line = advocacy: Short-term & long term outcomes

Vaccines
Food Safety
(Funding)
Food Prep
Food Handling

NASPGHAN ★★★ 2015
Annual Meeting & Postgraduate Course

“Naspys”
It’s Been a “Nutty Year” Award

October 7–11, 2015 • Washington Hilton • Washington, DC
Peanut Allergy

"USA prevalence quadrupled in 13 years - from 0.4% in 1997 to >2% in 2010"


2. Treatment reduces kids' peanut allergy risk up to 86%

3. Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

Du Toit, NEJM 372:803, 2015

The prevalence of peanut allergy among children has been rising dramatically. What's driven the increase? How can it be reversed? Findings from the LEAP study focusing on peanut consumption early in life are summarized in a short slide.

The LEAP Trial

The prevalence of peanut allergy among children has been rising dramatically. What's driven the increase? How can it be reversed? Findings from the LEAP study focusing on peanut consumption early in life are summarized in a short slide.
**Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy**

**Abstract**

**Background**

The prevalence of peanut allergy among children in Western countries has doubled in the past 20 years. We sought to determine whether early exposure to peanuts in infants at high risk would prevent peanut allergy.

**Methods**

We conducted a randomized clinical trial of peanut consumption in infants at high risk for peanut allergy. Infants (4–10 months) were randomized to consume or avoid peanuts until age 5 years. The primary end point was persistence of peanut allergy more than 12 months after randomization. The trial was designed to have 95% power to detect a 15% difference in the proportion of children with peanut allergy between the groups, with a 2-sided type 1 error of 0.05.

**Results**

At baseline, children with a negative skin-prick test to peanut had a 35% prevalence of peanut allergy, compared with 11% in children with a positive test (p < 0.001). The prevalence of peanut allergy was 14% in the avoidance group and 2% in the consumption group (p = 0.036).

**Conclusion**

In infants at high risk for peanut allergy, early exposure to peanuts until 60 months of age is effective in preventing development of peanut allergy.”

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**Prevalence of Peanut Allergy**

- **Negative skin-prick test at baseline**
  - Infants (4–10 mos) at high risk
  - Consume/avoid peanuts until 60 mos

  - **Avoid** 14%
  - **Consume** 2%
Prevalence of Peanut Allergy

Du Toit, NEJM 372:803, 2015

**Prevalence of Peanut Allergy**

<table>
<thead>
<tr>
<th>Negative skin-prick test at baseline</th>
<th>Positive skin-prick test at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid</td>
<td></td>
</tr>
<tr>
<td>14%</td>
<td>35%</td>
</tr>
</tbody>
</table>

**Gruchalla & Sampson, NEJM 372:803, 2015**

Preventing Peanut Allergy through Early Consumption: Ready for Prime Time?
Rebecca S. Gruchalla, M.D., Ph.D., and Hugh A. Sampson, M.D.

Kids can’t take peanut home to school. Some schools no longer allow peanut because of fear of anaphylaxis among peers. These decisions have become the leading cause of anaphylaxis and death related to food allergy in the United States.”

Fleischer, Pediatrics 136:600, 2015

“Landmark Study”

“has the potential to transform how we approach food allergy prevention”

Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-risk Infants

Fleischer, Pediatrics 136:600, 2015
Infections and Risk of Celiac Disease in Childhood: A Prospective Nationwide Cohort Study

Marild, Am J Gastroenterol (online) 8 October 2015

OBJECTIVES: Studies on early life infections and risk of later celiac disease (CD) are inconsistent but have mostly been limited to retrospective designs, is patient data, or insufficient statistical power. We aimed to test whether early life infections are associated with increased risk of later CD using prospective population-based data.

METHODS: This study, based on the Norwegian Mother and Child Cohort Study, includes prospective, repeated measurements of parent-reported infectious disease risks up to 18 months of age for 12,901 children born between 2000 and 2009. CD was identified through parental questionnaires and the Norwegian Patient Registry. Logistic regression was used to estimate odds ratios adjusted for child’s age and sex.

"...high infection frequency in first 18 mos = increased risk of later CD"

Additional files: upper respiratory tract infections: 1.53 (95% CI 1.25-1.88), lower respiratory tract infections: 1.25 (95% CI 1.06-1.49), and gastrointestinal infections: 1.55 (95% CI 1.36-1.78). Additional factors considered in the models were gestational age, sex, family history of celiac disease, parental metabolic syndrome, and birth hospital admission, both season and antibiotic treatment within 14 days prior gestation.

Infection frequency 6–18 months

X3 infections
4-5 infections
6-8 infections
X9 infections

Adjusted odds ratios (95% CI)

"...increasing risk according to number of infections"
"...increasing risk according to number of infections"

"NASPYS"
Question of the Year

Should we all go Gluten-Free???
Majority of Americans think gluten-free diet will boost health: study 63%

100 million consume a GFD

GLUTEN FREE MUSEUM

GLUTEN FREE MUSEUM
How to Become Gluten Intolerant

By Dr. Oster Schrabel - August 17, 2015

Ever wonder how you can become gluten intolerant even if you don’t actually have gluten intolerance or Celiac disease? We’ve found a video that describes how you can become gluten intolerant with some simple, non-descript statements and overly detailed medical symptoms that you can share on Facebook or your blog that nobody reads.

Becoming gluten intolerant is certainly the latest fad. Not eating meats used to be the only way to have a hip and in-style eating habit, but all of that has changed with gluten-free diets. “Being gluten intolerant is a fantastic opportunity to exert your dominance on the lives of everyone around you... which helps improve your life.”

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**Monday, May 16, 2011 12:00 AM - New York - The Wall Street Journal**

**Tennis**

**The Diet That Shook Up Tennis?**

Starchy Madness: Novak Djokovic’s Domination of the Sport Has Concocted With His Gluten-Free Turn

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**Monday, May 16, 2011 12:00 AM - New York - The Wall Street Journal**

**Tennis**

**The Diet That Shook Up Tennis?**

Starchy Madness: Novak Djokovic’s Domination of the Sport Has Concocted With His Gluten-Free Turn
Lis, Sport Nut & Exer Metab 25:37, 2015
Exploping the Popularity, Experiences, and Beliefs Surrounding Gluten-Free Diets in Nonceliac Athletes
Dana M. Lis, Trent Stellingswerff, Cecilia M. Shing, Kihan D.K. Ahuja, and James W. Fell

Adherence to a gluten-free diet (GFD) for nonceliac athletes (NCA) has become increasingly popular despite a paucity of supportive medical or exercise evidence. This study aimed to quantify the demographics of NCA and determine associated experiences, perceptions, and sources of information related to GFD. Materials and Methods: A survey was administered to 100 athletes. Forty-one percent of NCA respondents, including 18 World and/or Olympic medalists, indicated adherence to a GFD and provided reasons for doing so. Results: Self-diagnosed gluten sensitivity (6.5%) was the primary reason for adopting a GFD. Leading sources of GFD information were online (28.7%), personal contact (26.2%) and other athletes (17.4%). Although 59% of the general population is estimated to benefit clinically from a GFD, a higher prevalence of GFD adherence was found in NCA (41%). Prescription of GFD among non-athletes does not result from evidence-based

No Effects of a Short-Term Gluten-free Diet on Performance in Nonceliac Athletes.
Lis, Dana; Stellingswerff, Trent; Shing, Cecilia M.; Ahuja, Kihan D.K.; Fell, James

PURPOSE: Implementation of gluten-free diets amongst non-celiac athletes has rapidly increased in recent years due to perceived ergogenic and health benefits. The aim of this study was to investigate the effects of a gluten-free diet (GFD) on exercise performance, gastrointestinal (GI) symptoms, perceived well-being, emotional injury, and inflammatory responses in non-celiac athletes.

Lis, Med & Science in Sport & Exer (in press) 2015
Nonceliac Gluten Sensitivity

Fasano, Gastroenterology 148:1195, 2015

During the past decade there has been an impressive increase in popularity of the gluten-free diet (GF-D)—now the most trendy dietary habit in the United States and other countries. According to recent surveys, as many as 10% of all Americans without celiac disease report problems with a year. Owing to the concept that the GF-D benefits only individuals with celiac disease, health care professionals have struggled to separate the wheat from the chaff. There are claims that eliminating gluten from the organoleptic characteristics, and palatability. It is used unenriched into many foods, such as breads, pastas, pizza, bagels, breakfast, and drinks such as beer. Furthermore, the functional properties of gluten provide the ability to form gluten-free. The same characteristics that make gluten so unique and desirable for human consumption also lead to disease: the heat, wheat and celiac disease, are mediated by the wheat-enriched system. If you like this disease in

CD and NCGS are different clinical entities

Fasano, Gastroenterology 148:1195, 2015
CD and NCGS are different clinical entities
Fasano, Gastroenterology 148:1195, 2015

- NCGS - gluten-induced activation of innate, rather than adaptive, immune responses
- NCGS - absence of detectable changes in mucosal barrier function
- Don’t have the same long-term consequences

“Working” Definition of NCGS

GLUTEN FREE MUSEUM

“Working” Definition of NCGS

GLUTEN FREE MUSEUM
“Working” Definition of NCGS
Fasano, Gastroenterology 148:1195, 2015

“...clinical entity induced by ingestion of gluten leading to intestinal and/or extraintestinal symptoms that resolve once gluten is eliminated... CD & wheat allergy ruled out”

- Non-allergic, non-immune
- Defined by clinical symptoms only

Clinical Spectrum: Self-reported symptoms

GLUTEN FREE MUSEUM
Non-celiac gluten sensitivity

1. **GI symptoms:**
   - Abdominal pain, Reflux
   - Gas/bloating, Nausea
   - Diarrhea/constipation

2. **Non-GI symptoms:**
   - Headache, “Fatigued/Tired”
   - Anxiety, Depression
   - Rash, muscle aches, “numb”

**Relationship: Gluten ↔ IBS?**

GLUTEN FREE MUSEUM
Data?

Research Cristofori, JAMA Pediatr, 168:555, 2014

Original Investigation

Increased Prevalence of Celiac Disease Among Pediatric Patients With Irritable Bowel Syndrome: A 6-Year Prospective Cohort Study

Elena Cristofari, MD; Claudia Fantini, MD; Alessandro Magnoli, MD; Tommaso Caprioli, MD; Fiona Ikuta, MD; Stefania Castellani, MD; Luciano Canzani, MD; Raffaele Franchina, MD, PhD

BACKGROUND: Recurrent abdominal pain is a prevalent health issue in childhood. Clinical criteria (ie, the Rome criteria) have been established to aid diagnosis. Studies of adults have shown an increased prevalence of celiac disease among patients with irritable bowel syndrome (IBS). Few data are available with regard to children.

OBJECTIVE: To assess the prevalence of celiac disease among children with abdominal pain-related functional gastrointestinal disorders classified according to the Rome criteria.

DESIGN SETTING: PERSPECTIVE: A 6-year (2006-2012) prospective cohort study conducted in a tertiary referral center for the diagnosis and follow-up of gastrointestinal disorders in southern Italy (ie, Bari, Italy). A total of 992 children (42.2% male; median age, 6.9 years) consecutively referred for recurrent abdominal pain by their primary care physicians without previous investigation were evaluated.

992 children w/ RAP (Rome III); CD in:  
- 4.4% of IBS (OR = 4.2)  
- 1.0% of functional dyspepsia  
- 0.3% of functional abdominal pain

Consecutively referred for recurrent abdominal pain by their primary care physicians without previous investigation were evaluated.
GLUTEN ↔ NCGS?

Recall

• Several Studies which suggested an association:
  - Biesiekierski, Amer J Gastro 106:508, 2011
  - Vazquez-Roque, Gastro 144:903, 2013
Small Amounts of Gluten in Subjects With Suspected Nonceliac Gluten Sensitivity: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Trial

Antonio Di Sabatino, Umberto Volta, Chiara Salvatore, Paolo Biancheri, Giacomo Cai, Roberto De Giorgi, Michele Di Stefano, and Gino R. Corazza


Patients with non-celiac gluten sensitivity (NCGS) often benefit from a gluten-free diet (GFD). However, the role of gluten exposure in the condition is not fully understood. The study aimed to assess the effects of low gluten exposure on symptom improvement in NCGS.

Rationale:
There is debate over whether a gluten-free diet alone is sufficient for symptom improvement in NCGS. The role of gluten exposure in symptom exacerbation and the potential for symptom improvement with low gluten exposure are areas of interest.

Methods:
A prospective, randomized, double-blind, placebo-controlled, cross-over trial was conducted. Patients with NCGS were enrolled and divided into two groups: one group received a GFD, and the other received a gluten-containing diet (GCD). Both groups underwent a 3-month dietary intervention followed by a 3-month washout period. The primary outcome was symptom severity assessed using a validated symptom scoring system.

Results:
Symptom severity decreased significantly in both groups during the dietary interventions. However, the GFD group showed a greater reduction in symptom severity compared to the GCD group, indicating a potential beneficial effect of low gluten exposure.

Conclusion:
Low gluten exposure may have a positive impact on symptom improvement in patients with NCGS. Further research is needed to confirm these findings and to explore the optimal gluten exposure levels that can be tolerated without exacerbating symptoms.
Maybe Innocent!

Is improvement due to:
• Placebo (a healthier diet)?
• No Gluten, no Wheat?
• Less Fiber – less gas!

Other offenders!
Maybe Innocent
Is improvement due to:
• Placebo (a healthier diet)?
• No Gluten, no Wheat?
• Less Fiber – less gas!

Other offenders!

FODMAP Ingestion

Poorly absorbed carbohydrates

Fermentation

Excess gas/SCFA

GI Symptoms

Impact on Microbiome

Fermentable
Oligoaccharides
Disaccharides
Monosaccharides
And Sugar Alcohols
Polyols

Poorly absorbed carbohydrates

FODMAP Ingestion

Fermentable
Oligoaccharides
Disaccharides
Monosaccharides
And Sugar Alcohols
Polyols

Fermentable
Oligoaccharides
Disaccharides
Monosaccharides
And Sugar Alcohols
Polyols
A low FODMAP diet decreases abdominal pain frequency in IBS.

**Chumpitazi, Alimentary Pharmac and Therapeutics, 42:418, 2015**

**Biesiekierski, Gastroenterol 145:320, 2013**

No Effects of Gluten in Patients With Self-Reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-Chain Carbohydrates.


**Is it the wheat??**

**GLUTEN FREE MUSEUM**
Is it the wheat??

GLUTEN FREE MUSEUM

How could wheat cause GI sx?

Wheat

GI Symptoms

Wheat

Carbohydrates

Gluten

GI Symptoms
Nonceliac Gluten Sensitivity or Wheat Intolerance Syndrome?

Sofia Guandalini, MD, and Isabel Polanco, MD

The increase in world-wide consumption of a Mediterranean diet, which includes a wide range of wheat-based foods, has partly contributed to an alarming rise in the incidence of wheat (gluten) related disorders. Gluten, the main protein component in wheat, barley, and rye, is a mixture of alcohol insoluble (gliadins) and soluble (glutenins), proteins. Gliadins are a group of proteins and glutamine rich polypeptides resistant to digestion in the gastrointestinal tract.

Gluten consumption has been linked to a wide range of disorders, including celiac disease (CD), wheat allergy, dermatitis herpetiformis, gluten enteropathy, and possibly a "new" entity called "nonceliac gluten sensitivity." Systemic manifestations were most commonly found in the tongue, mouth, face, and extremities. In the gastrointestinal tract, the symptoms occurred within 2 hours after gluten ingestion in 65%, between 6 and 24 hours after ingestion, and on average less than 30% of patients reported the appearance of symptoms every time or often after the ingestion of gluten containing food. More than one-half of these patients, the symptoms occurred within 4 hours after gluten ingestion in 65%. Between 5% and 30% of patients with CD, CD in a double-blind gluten-controlled trial, which included 14 patients with CD, and symptoms controlled with a gluten-free diet.

Wheat Intolerance Syndrome

• Broader term
• Reflects objective elements:
  1. Causative role of Wheat (not gluten)
  2. “Intolerance” not sensitivity
  3. “umbrella” - series of symptoms due to various causes

How do we evaluate!

How do we evaluate!

1. R/O celiac disease
2. R/O wheat allergy
3. R/O other food intolerances
4. Individualize dietary strategy (FODMAP, wheat, etc.)
5. Avoid the hype!
Future Needs:

1. Well defined nosology for wheat/gluten-related disorders
2. Phenotypes and mechanisms of syndromes responsive to gluten (wheat) withdrawal defined
3. Definitive therapy
4. Biomarkers to separate:
Winners of the Ig® Nobel Prize
For achievements that first make people LAUGH then make them THINK

Rubio, Food Microbiology, 38:303, 2014
Bacteria isolated from infant diapers used to ferment meat “...make delicious sausages”
Pooperoni Challenge of the Year Each

NASPGHAN ★☆☆ 2015 Annual Meeting & Postgraduate Course

“NASPYS” Challenge of the Year Each

October 7–11, 2015 • Washington Hilton • Washington, DC

The New York Times Business Day

A.M.A. Recognizes Obesity as a Disease
NASH prevalence increased by 170% in registrants listed for liver transplant

Wong, Gastroenterology 148:547, 2014

• 330 patients; age @ LT = 4 to 40 yrs
• 4% <18 yo and 6% were 18-25 yo

Alkhouri, Transplant Int September 24, 2015 (in press)
Challenges

1. What is the Mechanism?
2. What are the Complications?
3. NAFLD?
   - Prevalence
   - Diagnosis
   - Treatment

Liver Transplantation for Nonalcoholic Steatohepatitis (NASH) in Young Patients

Alkhouri, Transplant Int September 24, 2015 (in press)

- F/U (~4 yrs) 30% died
- 12% re-transplanted
- 34% for NASH recurrence
Challenges

1. What is the Mechanism?
2. What are the Complications?
3. NAFLD:
   - Prevalence
   - Diagnosis
   - Treatment
   - Most common:
     - Diet
     - Sleep
     - Activity
     - Rare = monogenic causes

Complex

Challenges

1. What is the Mechanism?
2. What are the Complications?
3. NAFLD:
   - Prevalence
   - Diagnosis
   - Treatment
   - Most common:
     - Diet
     - Sleep
     - Activity
     - Rare = monogenic causes

Complex

Monogenic causes (rare)

Ramachandrappa, JCI 121:2080, 2011
1. Leptin deficiency
2. Leptin receptor deficiency
3. POMC deficiency
4. MC4R deficiency
5. FTO mutations
6. others

BRIEF REPORT
THE NEW ENGLAND JOURNAL OF MEDICINE
Biologically Inactive Leptin and Early-Onset Extreme Obesity
Martin Wabitsch, M.D., Ph.D.; Jürgen Fröhlich, M.D.; Belinda Lennert, M.D.; Ursula Kohlmeier-Kahl, M.D.; Georgia Labic, Ph.D.; Klaus-Michael Debatin, M.D.; Petra Vatter, Ph.D.; Peter Gerschik, M.D.; Barbara Moepps, Ph.D.; and Daniela Farkas Respondek, Ph.D.
Wabitsch, NEJM 372:48, 2015

SUMMARY

Mutations in the gene encoding leptin (LEP) typically lead to an absence of circulating leptin and to extreme obesity. We describe a 2-year-old boy with early-onset extreme obesity due to a novel homozygous transversion (L2903=1) in LEP, leading to a change from aspartic acid to tyrosine at amino acid position 360 (p.G130R) and high immunoreactive levels of leptin. Overexpression studies confirmed that the mutant protein is secreted but neither binds to nor activates the leptin receptor. The mutant protein failed to reduce food intake and body weight in leptin-deficient ob/ob mice. Treatment of the patient with recombinant human leptin (Nutrelpa) rapidly normalized eating behavior and reduced in weight loss.
- 2-yo early-onset extreme obesity

Leptin mutant did not bind nor activate leptin receptor

Treatment of patient with leptin normalized eating behavior and resulted in weight loss
Challenges

1. What is the Mechanism?
2. What are the Complications?
3. NAFLD:
   - Prevalence
   - Diagnosis
   - Treatment

MRI scan: obesity impacts every organ!
MRI scan: obesity impacts every organ!

Skinner, NEJM 373:1307, Oct 1, 2015
Cardiometabolic Risks and Severity of Obesity in Children and Young Adults

Abstract
The prevalence of severe obesity among children and young adults has increased over the past decade. Although the prevalence of cardiometabolic risk factors is relatively low among children and young adults who are overweight or obese, those with more severe forms of obesity may be at greater risk.
Baseline prevalence - predictors of CVD (risk factor):
– fasting hyperinsulinemia (74%)
– elevated CRP (75%)
– dyslipidemia (50%)
– elevated BP (49%)

Cardiometabolic risk factors associated with NAFLD severity
– elevated CRP (75%)
– dyslipidemia (50%)
– elevated BP (49%)
Afx Well: Are Fatty Liver and Sleep Apnea Related?

The New York Times

YES - Minville, CHEST 145:525, 2014

The Journal of Pediatrics • www.jpeds.com

Obstructive Sleep Apnea and Hypoxemia Are Associated with Advanced Liver Histology in Pediatric Nonalcoholic Fatty Liver Disease

Srikho S. Sundaram, MD, MSCI; Ronald J. Sokol, MD; Kelley E. Capocci, MD; Zhehong Pan, PhD; Jillian S. Sullivan, MD; Nordin Masri, MD; and Ali C. Alburey, MD

Objective: To determine whether obstructive sleep apnea (OSA) and/or nocturnal hypoxemia are associated with the severity of liver injury in patients with pediatric nonalcoholic fatty liver disease (NAFLD).

Study design: Obese children aged 10-18 years with liver biopsy-proven NAFLD were enrolled. Demographic, clinical, and laboratory data were collected, polysomnography was performed, and liver histology was scored. Subjects were divided into those with OSA/hypoxemia and those without OSA/hypoxemia for analysis.

Results: Of 70 subjects with NAFLD, OSA/hypoxemia was present in 19 (27%) (mean age, 12.8 ± 1.9 years; 68% male; BMI 30.6 ± 3.0). Subjects with and without OSA/hypoxemia had similar levels of serum aminotransferases, serum leptin, and inflammatory and insulin resistance markers. Although there were no differences between groups in the histological severity of steatosis, in inflammation, ballooning degeneration, NAFLD activity score, or histological grades, subjects with OSA/hypoxemia had significantly more severe hepatic fibrosis. Moreover, oxygen saturation nadir during polysomnography was related to hepatic fibrosis stage (P = 0.05; P < 0.01) and aspartate aminotransferase level (P = 0.02; P = 0.05). Increasing percentage of time with oxygen saturation <90% was related to NAFLD inflammation grade (P = 0.04; P = 0.03), degree of hepatic steatosis (P = 0.002; P < 0.001), NAFLD activity score (P = 0.01; P < 0.001), aspartate aminotransferase level (P = 0.06; P < 0.001), and platelet to aminotransferase level (P = 0.44; P < 0.001).

Conclusion: Moderate OSA/hypoxemia is common in pediatric patients with biopsy-proven NAFLD. OSA and the severity/duration of hypoxemia are associated with biochemical and histological measures of NAFLD severity.
MRI scan: obesity impacts every organ!
"Nonalcoholic Fatty Pancreas Disease (NAFPD)"

DellaCorte, Clin Endocrinol, in press, Oct 2015

- 121 children w/ NAFLD:
- 48% had ectopic accumulation of fat in pancreas (NAFPD)
- Significantly higher BMI, higher insulin levels/insulin resistance
Schwimmer, HEPATOLOGY 61:1887, 2015

Magnetic Resonance Imaging and Liver Histology as Biomarkers of Hepatic Steatosis in Children With Nonalcoholic Fatty Liver Disease

Jeffrey R. Schwimmer,1,3* Michael S. Middeldorp,2 Gerlinde Belding,1,3 Similarly E. Newton,1,3
Benneth J. Jones,2,3 Melissa X. Pats,1 Jessica Iani,1,4 Jonathan C. Hacker,2 Garth Huddleston,1
John Juvik,1,3,4 and Gadde H. Ylvisaker1

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children. In order to advance the field of NAFLD, noninvasive imaging methods for diagnosis of NAFLD

Compared MRI estimated proton density fat fraction (PDFF) to histology (n = 174 children)

MRI estimated liver PDFF and severity grade was influenced by both sex and thread stage. The correlation was significantly (P < 0.001) stronger in girls (r = 0.86) than in boys (r = 0.78). The correlation was significantly (P < 0.001) weaker in children with stage 2-4.
Excellent correlation between PDFF & liver fat content (steatosis grade)

Grade 0
PDFF 2%

Grade 1
PDFF 14%

Grade 2
PDFF 21%
Excellent correlation between PDFF & liver fat content (steatosis grade)

Grade 0  Grade 1  Grade 2  Grade 3
PDFF 2%  PDFF 14%  PDFF 21%  PDFF 31%

...superiority of MR-based methods (both MRI, MRS) over ultrasound is clear
...won't replace Liver Biopsy
Assess Liver Stiffness; Correlates with fibrosis

Xanthakos, J Peds 164:186, 2014

Use of Magnetic Resonance Elastography to Assess Hepatic Fibrosis in Children with Chronic Liver Disease

Steven A. Xanthakos, MD, MS; Daniel N. Pedersen, MD; Serhiy Sereny, PhD; Lily Lin, MD; Ellen C. King, PhD; William F. Baden, MD; and Robert Kaul, MD, MS

Management of pediatric chronic liver disease is limited by lack of validated noninvasive biomarkers of histologic severity. We demonstrate that magnetic resonance elastography is feasible and accurate in detecting significant hepatic fibrosis in a case series of 35 children with chronic liver disease, including severely obese children. (Pediatr 2014;164:186.)

Xanthakos, J Peds 164:186, 2014

Loomba, Hepatology 60:1920, 2014

Magnetic Resonance Elastography Predicts Advanced Fibrosis in Patients With Nonalcoholic Fatty Liver Disease: A Prospective Study

Robin Loomba,3,6,8,10,11 Tara Wolthers,3,6 Brendan Ang,3 Jonathan Blosser,6,8,10,11 Gotham Binning,3,6 Michael Peterson,3,6,11 Mark Vavilala,3,6 Grace Lin,3 David Benson,3,6,11 Audrey Garg,3,6,11 Richard Elkan,3,6,11 and Claude Lefebvre3,6,8,10,11

Retrospective studies have shown that two-dimensional magnetic resonance elastography (2D-MRE), a novel MR method for assessment of liver stiffness, correlates with advanced fibrosis in patients with nonalcoholic fatty liver disease (NAFLD). Prospective data on diagnostic accuracy of 2D-MRE in the detection of advanced fibrosis in NAFLD are limited. The aim of this study is to prospectively assess the diagnostic accuracy of 2D-MRE, a noninvasive imaging technique, in predicting advanced fibrosis (stage 3 or 4) in well-characterized patients with biopsy-proven NAFLD.

Loomba, Hepatology 60:1920, 2014
Stage 0  Stage 1  Stage 2
1.7 kPa  2.1 kPa  3.2 kPa

Stage 0  Stage 1  Stage 2  Stage 3
1.7 kPa  2.1 kPa  3.2 kPa  6.2 kPa
Loomba, Hepatology 60:1920, 2014

Magnetic Resonance Elastography Predicts Advanced Fibrosis in Patients With Nonalcoholic Fatty Liver Disease: A Prospective Study

Stage 0 | Stage 1 | Stage 2 | Stage 3 | Stage 4
---|---|---|---|---
1.7 kPa | 2.1 kPa | 3.2 kPa | 6.2 kPa | 6.9 kPa

“What can we do to prevent?”

- Life-style (Eat, Move, Sleep, Pray!)

“Avoid” antibiotics

“Avoid” sugar-sweetened beverages

Cox, Cell 158:705, 2014


Bailey, JAMA Pediatrics, 168:1063, 2014
“What can we do to prevent?”

- Life-style (Eat, Move, Sleep, Pray!)

- Avoid sugar-sweetened beverages

- Avoid antibiotics


**Our Chairs Are Killing Us**

>5hrs/day = ↑ risk of NAFLD

September 15, 2015


...positive relationship

“What can we do to prevent?”

- Life-style (Eat, Move, Sleep, Pray!)

Short sleep duration in early childhood independently associated with obesity

Bonuck, J. Pediatr. 166:632, 2014

All 3 = sedentary time positively assoc. with obesity & NAFLD
attain at least 55 min of physical activity/day

You snooze, you lose.

Physical Activity, Sedentary Time, and Obesity in an International Sample of Children

Exploring the Adolescent Activity-Related Physical Health Correlates of Sleep Duration
Ali McManus, Philip N Ainslie, Daniel J Green, Ryan G Samani, Kurt Smith
McManus, Experimental Physiology (in press - October 2015)

Avoid antibiotics
Cox, Cell 158:705, 2014

Avoid sugar-sweetened beverages

Life-style (Eat, Move, Sleep, Pray!)

You snooze, you lose.

“You snooze, you lose.”

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“You snooze, you lose.”

“You snooze, you lose.”

“You snooze, you lose.”

“You snooze, you lose.”

“You snooze, you lose.”
Late bedtimes for teens could lead to weight gain over time

"adolescent bedtimes, not just total sleep time, a potential target for weight management"

Asarnow, SLEEP 38:1523, 2015

POSSIBLE LINK BETWEEN BEDTIME AND CHANGE IN BODY MASS INDEX

Evidence for a Possible Link between Bedtime and Change in Body Mass Index

Evidence for a Possible Link between Bedtime and Change in Body Mass Index

every hour of sleep lost = 2.1 point increase in BMI
“What can we do to prevent?”

- Life-style (Eat, Move, Sleep, Pray!)
- Avoid sugar-sweetened beverages

The New York Times

October 4, 2015

The Decline of ‘Big Soda’

The drop in soda consumption represents the single largest change in the American diet in the last decade.

www.nytimes.com

www.nytimes.com

10-4-15
"What can we do to prevent?"

- Life-style (Eat, Move, Sleep, Pray!)
- Avoid sugar-sweetened beverages
- “Avoid” antibiotics
  - Cox, Cell 158:705, 2014

"What can we do to treat?"

- Probiotics / Prebiotics
- Fatty Acids (Omega-3, DHA)
- Antioxidants (Vitamin E)
- Antifibrotics
- BARIATRIC approaches
- ? Pharmacologic
Another Agent for Obesity — Will This Time Be Different?
(Ehsan S. Siraj, M.D., and Kevin Jon Williams, M.D.)

Over the past few decades, obesity has become a global epidemic that affects diverse societies across developed and developing countries. Obesity rates correlate well with recent developments such as increased affluence to sit and an unprecedented availability, at low or no cost, of foods and beverages rich in poorly satiating calories. These rapid environmental changes intersect with preexisting genetic tendencies, yet a time.

Obesity remains limited because of side effects and inadequate efficacy, especially in the long-term. Bariatric surgery results in the most weight loss and the highest rates of remission of type 2 diabetes, but the potential side effects are of concern. Furthermore, performing bariatric surgery is approximately 400 million obese persons worldwide is not feasible.

Enter another approach: glucagon-like peptide-

The NEW ENGLAND JOURNAL of MEDICINE

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Kazer Pi-Sunyer, M.D., Anne Aronov, M.D., D.M.S., Ken Fujikawa, M.D., Frank Gower, M.D., Alfredo Hijar, M.D., Michael Engelfriet, M.D., Ph.D., David C.W. Jia, M.D., Ph.D., Carol W. Kieffer, F.A.C.P., Ph.D., Richard Vincent Ong, M.D., Christine Ryan-Jones, M.D., Ph.D., and John P.W. Wilding, M.D., F.A.C.P.

Pi-Sunyer, NEJM 373:11, 2015

Glucagon-like peptide-1 analogue
“mimics effects of satiety hormone”

Weight Loss
Obeticholic acid for the treatment of fatty liver disease—NASH no more?


The quest for effective agents to treat NASH has moved a step forward with the demonstration that treatment with obeticholic acid can improve the histological features of the disease, with reported antifibrotic activity.

NASH, which encompasses a spectrum of disease from simple steatosis to NASH, fibrosis and cirrhosis, is becoming increasingly common worldwide. With no approved agents for NASH or NASH currently available, NAFLD is predicted to become the primary cause of end-stage liver disease and need for liver transplantation ahead of viral hepatitis. NASH in particular is a more progressive form of NAFLD, and NASH progresses so rapidly that the cirrhosis end stage is reached within five years in many cases. First-line therapy for NASH is weight loss and moderate exercise. If that fails, the second-line treatment is a combination of pioglitazone (Actos) and metformin (Glucophage). A third-line treatment is ursodeoxycholic acid, a bile acid that stimulates the bile acid synthesis pathway. If none of these therapies work, a toxicology study has shown that the liver-lung transplant procedure, which has been used to treat young patients with fulminant hepatic failure, can extend the lifespan of some patients.

Obeticholic acid (BG-12) is a bile acid derivative that selectively binds to the farnesoid X nuclear receptor (FXR). FXR, an important regulatory mediator of the gut-liver axis, regulates the production of bile acids and lipids from the liver. In patients with NASH, obeticholic acid significantly improved liver histology compared with placebo, particularly in those with fibrosis.

In the primary intention-to-treat analysis, 80 of 110 (45%) patients in the obeticholic acid group had improved liver histology compared with only 23 of 109 (21%) in the placebo group (relative risk 1.9, 95% CI 1.3–2.8, P=0.002); a 2-point or more improvement in the NAFLD activity score was recorded without worsening of fibrosis. Compared with controls, more patients receiving obeticholic acid had improvements in steatosis, hepatocellular ballooning, lobular inflammation and fibrosis. However, despite these improvements in liver histology, only a minority of patients had complete resolution of NASH.

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial


Summary

The farnesoid X nuclear receptor (FXR) regulates bile acid synthesis and its activation can have beneficial effects on liver disease. The aim of this study was to evaluate the safety, tolerability, and efficacy of obeticholic acid, a FXR agonist, in patients with non-cirrhotic, non-alcoholic steatohepatitis (NASH). The primary outcome was a ≥2-point improvement in a validated steatohepatitis activity index (SALT), ≥1-point improvement in the Metavir fibrosis score, and ≥2% reduction in body weight at 16 weeks.

Methods

A multicentre, randomised, double-blind, placebo-controlled trial was conducted in 190 NASH patients with a Body Mass Index (BMI) ≥30 kg/m², evidence of fibrosis by liver biopsy, and NAFLD activity score ≥4 (moderate to severe). The primary outcome was measured at 16 weeks and the secondary endpoints were measured at 16 weeks and 52 weeks.

Results

At 16 weeks, 52% of patients in the obeticholic acid group achieved the primary endpoint compared with 9% in the placebo group (P<0.0001). The secondary endpoints were also significantly improved in the obeticholic acid group compared with the placebo group. No new safety signals were identified.

Conclusions

Obeticholic acid is safe and effective in NASH patients with fibrosis and can improve liver histology, liver function, and body weight.

Clinical trial information

NCT01265491

Follow-up

Patients were followed for up to 52 weeks and the primary endpoint was repeated at 52 weeks.
Obeticholic Acid

NASH (fibrosis) improved

47% vs. 21%

≥ 90% of adolescent bariatric procedures

Now >70% of our pts

Questions:

When?

Who?

What?

Outcomes?
• 4-PB retargets mutated BSEP in pts with PFIC2
• Bile secretion & PRURITUS improve

Before 4-PB therapy - Septal fibrosis

3 mos after 4-PB therapy
Carbamazepine

The classic form of α1-antitrypsin deficiency (A1AD) is a well-known genetic cause of severe liver disease in childhood. A point mutation affects the folding of hepatic secretory glycoprotein such that the protein is prone to misfolding and polymerization. Liver injury is characterized by subendothelial deposition of fibrous tissue and cirrhosis, caused by trapping of misfolded α1-antitrypsin. The variant forms of A1AD, including a classic form in which a point mutation leads to altered folding during biogenesis. In this classic form, the mature protein, α1-antitrypsin (A1AT), accumulates in the endoplasmic reticulum (ER) of hepatic intracellular pathways have been shown to be dysregulated in A1AD. As A1AT accumulates in the ER, it triggers the regulated degradation of misfolded protein. Recently, we have found that drugs that inhibit the autophagy pathway reduce the collagen content and improve hepatic fibrosis in a mouse model.

Lysosomal Lipase Deficiency — A New Therapy for a Genetic Lipid Disease

Daniel J. Rader, M.D.

There are more than 50 different lysosomal storage diseases, genetic disorders characterized by lysosomal accumulation of substrates. Phenotypes vary widely, depending on the specific cell type affected. Enzyme-replacement therapy has been successful in the treatment of these diseases, but enzyme replacement therapy is currently approved for only 7 lysosomal diseases. The principle of enzyme replacement is that after administration of a recombinant protein, it is taken up by target cells via

Lysosomal Acid Lipase Deficiency — An under-recognized cause of dyslipidaemia and liver dysfunction

Zeljko Reiner, Stefano Benoni, Terence Egan, John Harris, Sally A. Beale, Kees Hoek, and Brian Weise

Lysosomal acid lipase deficiency (LAL-D) is an autosomal recessive disorder caused by mutations in the LIPA gene that lead to deficient activity of lysosomal acid lipase

Atherosclerosis

Zeljko Reiner, Stefano Benoni, Terence Egan, John Harris, Sally A. Beale, Kees Hoek, and Brian Weise

Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipid-laden foam cells in the walls of arteries. It is a major cause of morbidity and mortality worldwide. Lysosomal acid lipase deficiency (LAL-D) is an autosomal recessive disorder caused by mutations in the LIPA gene that lead to deficient activity of lysosomal acid lipase. LAL-D is characterized by the accumulation of lipids in various tissues, including the liver, lung, and arteries, leading to organ dysfunction.

Carbamazepine

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Clinical Features of Lysosomal Acid Lipase Deficiency – a Longitudinal Assessment of 48 Children and Adults

Authors:
Barbara K. Burton, MD; Patrick B. Deegan, MD; Gregory M. Enns, MD; Omella Guarigliamagna, MD; Simon Horslen, MB, CHB, FRCPCH; Gerald K. Hovingh, MD; Steve J. Lobatto, MD; Vera Malinova, MD; Valeria A. McLean, MD; Julian Rainman, MD; Maja Di Rocco, MD; Sanja Santra, MD; Reena Sharma, MBBS; Jostern Sylven-Cegielska, MD; Clue B. Whitley, MD; Stephen Eckert, PHD; Vasili Valayamkondah, MD; Anthony G. Quinn, MBCS PDP FRCP*.

Burton, JPGN, in press Oct 2015

• Serum ALT elevated in 92%
• Elevated LDL (64%); low HDL (44%)
• Steatosis (87%) and/or fibrosis (52%)

Burton, JPGN, in press Oct 2015
A Phase 3 Trial of Sebelipase Alfa in Lysosomal Acid Lipase Deficiency

The first enzyme replacement therapy that specifically targets hepatocytes

**ALT**

**LDL Cholesterol**
HDL Cholesterol

Hepatic FAT content
(Baseline to week 20)
Don’t Forget the Pancreas!

Progress, Opportunities, Challenges, Collaborations

- NASPghan Pancreas Committee
**Progress, Opportunities, Challenges, Collaborations**

- NASPGHAN Pancreas Committee
- Guidelines
- Studies

**Clinical Report**

**ESPGHAN and NASPGHAN Report on the Assessment of Exocrine Pancreatic Function and Pancreatitis in Children**

Christopher J. Taylor, Kathy Chen, Randy Harsch, David Hughes, David E. Leman, Abraham I. Gross, Jeremy Strauss, Mike Thompson, Stephanie Yan Butters, Manoj J. Verlaine, Shokai Z. Handa, and Michael Wackenell

Taylor, JPGN 61:144, 2015

**Abstract**

The purpose of this clinical report is to discuss recent advances in assessing exocrine pancreatic function (EPF) and provide an update on current clinical practice for differentiating acute and chronic pancreatitis, evaluating pancreatic exocrine function, and providing outcome and treatment recommendations. Key Words: exocrine pancreatic insufficiency, pancreatic exams, pancreatic exocrine function, chronic pancreatitis.

Throughout development, the pancreas maintains a close relationship with the liver, and it is essential for normal liver development and function. The pancreas is composed of acinar cells that secrete digestive enzymes, islet cells that secrete hormones, and ductal cells that transport enzymes and hormones. The pancreas is innervated by sympathetic and parasympathetic fibers, and afferent fibers that innervate the enteric nervous system (ENS) and secrete gastrin, secretin, hormones released by L-cells and S-cells, respectively. In the neonatal period of the small intestine, Paneth cells are present, and their function is essential for normal development and function.


Progress, Opportunities, Challenges, Collaborations

- NASPghan Pancreas Committee
- Guidelines
- Studies
- INSPIRE (Pancreas)

- The International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPIRE) consortium:
**Goal = develop Rx for recurrent acute and chronic pancreatitis in children**

**Risk factors for pancreatitis**

- **Genetic**
  - PRSS1 67%
  - SPINK1 19%
  - CFTR 14%
  - CTRC 3%
- **Autoimmune** 4%
- **Obstructive**
  - Pancreas divisum 33%
  - Sphincter of Oddi dysfunction 20%
  - Gallstones 1%
- **Toxic/metabolic**
  - Alcohol (determined by doctor) 1%
  - Passive smoking (exposure) 4%
  - Hyperlipidemia, Meds, Metabolic disease 1% each
- **None cited** 11%
Opportunity for the Future

Biliary Atresia: Forgotten...but Not Gone!
Biliary atresia is the most common indication for liver transplantation in the pediatric population and the most frequent liver-related cause of death in early childhood. However, in some cases, long-term survival with the native liver can be achieved by surgical reestablishment of bile flow. The procedure of choice involves removal of the fibrotic, atretic bile duct segment and construction of a drainage route via hepatoportoenterostomy (the Kasai procedure). The outcome following hepatoportoenterostomy is closely related to the age at the procedure. It is universally acknowledged that the earlier the diagnosis is established, the more likely that the child will avoid liver transplantation. It is late referral of patients for this potentially curative procedure that is considered as one of the main reasons for poor outcome—a reliable clue that can help detect the disease in the first month after birth is the yellow color of the stools (bileless stools). The procedure was introduced to Japan in 1957 by Dr. Shigeo Kasai, who proposed a new treatment for surgical reestablishment of bile flow. Kasai performed the procedure shortly after birth and the outcome was excellent. This was a breakthrough in the treatment of children with biliary atresia and, since then, the procedure has been widely used worldwide. However, the cost of the procedure is high and many countries cannot afford it.

**Early diagnosis of biliary atresia**

William F. Balister, MD

*J Pediatr 166:784, 2015*

**Goal: Establish diagnosis before 45 days of life**

**Newborn Screen Can Detect Biliary Atresia**

A check out today's newborn screening and you can identify biliary atresia in newborns, with high sensitivity and low false positives. The procedure is performed at birth, and is based on a combination of red blood cell and white blood cell counts. The red blood cell count is very high, while the white blood cell count is very low in newborns with biliary atresia. If the red cell count is above 700,000 cells/mm³, it is not due to biliary atresia, while if it is below 200,000 cells/mm³, it is due to biliary atresia. The condition appears to be effective especially in detecting the disease at a later stage. The screening can also help identify newborns with other problems that may be associated with biliary atresia. Using red cell counts, a screening test with high sensitivity and low false positives has been developed. The test is simple, non-invasive, and can be performed in the first month of life. It is recommended for all newborns, but especially for those born to mothers with a history of biliary atresia.

**The Journal of Pediatrics • www.peds.com**

**Gu, J Pediatrics 166:897, 2015**

**Stool Color Card Screening for Early Detection of Biliary Atresia and Long-Term Native Liver Survival: A 19-Year Cohort Study in Japan**

Yasunori Gu, MD, Wei-Lih, MD, Tatsuya Yata, MD, PhD, Tohru Kurokawa, MD, PhD, Tomoko Japanese, MD, PhD, Masaki Naka, MD, PhD, Junya Tanaka, MD, PhD, Takamasa Hayashi, MD, PhD, and Yuki Nakai, MD, PhD

**Objective** To evaluate the sensitivity and specificity of a stool color card used for a mass screening of biliary atresia conducted over 19 years. In addition, the age of Kasai procedure and the long-term probabilities of native liver survival were investigated.

**Study design** A total of 1,165 patients with biliary atresia were diagnosed. The sensitivity and specificity of stool color card screening at the 1-month check-up were 76.3% (95% CI 72.0-80.5) and 98.9% (94.5-99.9), respectively. Mean age at the time of Kasai procedure was 16.9 months. According to Kaplan-Meier analysis, the native liver survival probability at 5, 10, and 15 years was 87.5%, 78.5%, and 68.5%, respectively. The sensitivity and specificity of the stool color card were demonstrated by a 19-year cohort study. We found that the timing of Kasai procedure and long-term native liver survival rates were improved, suggesting the beneficial effect of stool color card screening. (J Pediatr 2015;166:897-902.)
<table>
<thead>
<tr>
<th>After the 1 month visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of completion</td>
</tr>
<tr>
<td>(Year/Month/Day)</td>
</tr>
<tr>
<td>Today's stool color was</td>
</tr>
<tr>
<td>closest to number (</td>
</tr>
<tr>
<td>Child's name</td>
</tr>
<tr>
<td>Child's birth date</td>
</tr>
<tr>
<td>Mother's name</td>
</tr>
<tr>
<td>Current address</td>
</tr>
<tr>
<td>Postal code</td>
</tr>
<tr>
<td>Phone number</td>
</tr>
</tbody>
</table>

- 313,230 infants screened
- 34 with biliary atresia
- Specificity @ one-mo check - 99.9%
- Mean age @ Kasai (59.7 days)

---

**Mogul, JPGN 60:91, 2015**

Cost-Effective Analysis of Screening for Biliary Atresia With the Stool Color Card

*Douglas Mogul, Yeh Zhou, Paul Justher, Kathleen Schwartz, and Kevin Frick*

**Abstract**

"...screening with stool color card... economically feasible strategy for improving outcomes in the USA..."
Color recognition software allows parents to photo their baby's stool

"Do we know what causes Biliary Atresia?"
Etiology of Biliary Atresia unknown
Balistreri, Hepatology 23:1682, 1996
Asai, Nat Rev Gastro Hepatol 12:342, 2015

• However, evidence implicating an environmental exposure:
  – infectious or toxic
  – in genetically susceptible individuals

? An Environmental Toxin as a Trigger

Time-space clustering

? An Environmental Toxin

• Coincide with maternal consumption of *Dysphania plant* (due to drought conditions)

Time-space clustering
Identification of a plant isoflavonoid that causes biliary atresia

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Biliary atresia (BA) is a rapidly progressive and destructive fibrotic disorder of unknown etiology affecting the extrahepatic biliary tree of neonates. Epidemiological studies suggest that an environmental factor, such as a virus or toxin, is the cause of the disease, although none have been definitively established. Several naturally occurring outbreaks of BA in Australian livestock have been associated with the ingestion of unusual plants by perinatal animals. These findings provide direct evidence that BA could be initiated by perinatal exposure to an environmental toxin.

• Imported *Dysphania* from pastures grazed on during the 2007 outbreak.

An Extrahepatic Biliary Toxin

• Used a zebrafish biliary secretion assay to isolate a novel phytosterol toxin
• “*biliatresone*”
• Led to selective destruction of extrahepatic bile ducts in larval zebrafish

Control

Intestinal excretion

*Biliatresone treated*

Gallbladder absent

Intestinal exc., reduced


Intestinal excretion

*Gallbladder*
Human biliary atresia initiated by perinatal exposure to a toxin?

- Human microbiota produces a metabolite of soy products similar to biliatresone
- Combine with genetic susceptibility to trigger human biliary atresia?

Asai, Nat Rev Gastro Hepatol 12:342, 2015

A way to prevent Biliary Atresia

That would really be...
“...never grow old, never cease to stand like a curious child before the great mysteries into which we were born”

- Albert Einstein -

“You may find someone who can do the job better than me, but you will never find someone who had more fun doing it"

Bill Clinton
Jan 2001