# Clinical Science: Year in Review 2015

# What's Hot?

William F. Balistreri, M.D.


Cincinnati Children's Hospital Medical Center

## Goal: Uncover….


"What's Trending" Articles published since we met last October

## Disclaimer

The Washington Post

Speaking of Science May 20, 2015

Why giant pandas have to eat and poop all day

The Washington Post

Speaking of Science May 20, 2015

Why giant pandas have to eat and poop all day

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

Bam-boo ⟶ Bam-poo

The Washington Post

Speaking of Science May 20, 2015

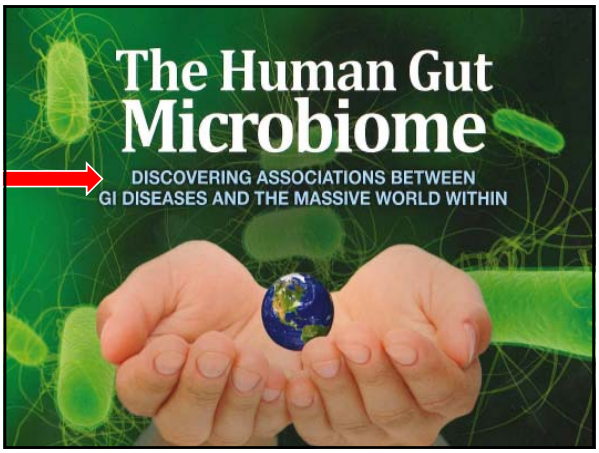
Why giant pandas have to eat and poop all day

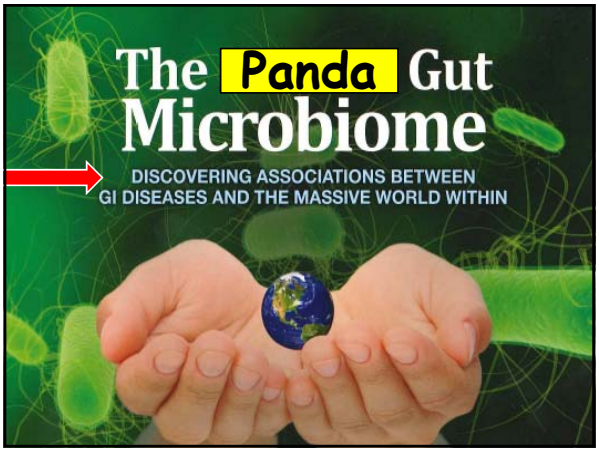
So….how do we know this?

….and what's it got to do with GI??

…eat each day!

Bam-boo ⟶ Bam-poo


The Human Gut Microbiome
DISCOVERING ASSOCIATIONS BETWEEN
GI DISEASES AND THE MASSIVE WORLD WITHIN


The Panda Gut Microbiome
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www.nature.com/scientificreports
Li, Scientific Reports 5:10185, 2015
SCIENTIFIC REPORTS
The evolution of the gut microbiota in the giant and the red pandas
Both herbivores

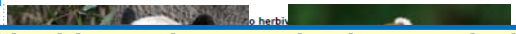
www.nature.com/scientificreports

*Li, Scientific Reports 5:10185, 2015*

SCIENTIFIC REPORTS

## The evolution of the gut microbiota in the giant and the red pandas

**Both herbivores**



**"herbivores have evolved anatomically specialized guts to efficiently deconstruct fibrous plant matter"**
**NOT the panda - "they lack cellulose-digesting enzymes"**

RESEARCH ARTICLE

*Xue, mBio 6:e00022-15, 2015*

## The Bamboo-Eating Giant Panda Harbors a Carnivore-Like Gut Microbiota

Zhengsheng Xue,[a] Wenping Zhang,[b] Linghua Wang,[a] Rong Hou,[b] Menghui Zhang,[a] Lisong Fei,[b] Xiaojun Zhang,[a] He Huang,[b] Laura C. Bridgewater,[a] Yi Jiang,[c] Chenglin Jiang,[c] Liping Zhao,[a,d] Xiaoyan Pang,[a] Zhihe Zhang[b]

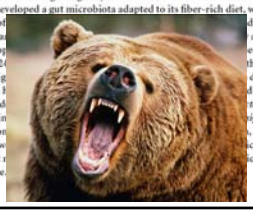
State Key Laboratory of Microbial Metabolism, School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Shanghai, People's Republic of China[a]; Sichuan Key Laboratory of Conservation Biology on Endangered Wildlife, Chengdu Research Base of Giant Panda Breeding, Chengdu, People's Republic of China[b]; Yunnan Institute of Microbiology, Yunnan University, Kunming, People's Republic of China[c]; Ministry of Education Key Laboratory of Systems Biomedicine, Shanghai Centre for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, People's Republic of China[d]

**ABSTRACT** The giant panda evolved from omnivorous bears. It lives on a bamboo-dominated diet at present, but it still retains a typical carnivorous digestive system and is genetically deficient in cellulose-digesting enzymes. To find out whether this endangered mammalian species, like other herbivores, has successfully developed a gut microbiota adapted to its fiber-rich diet, we conducted a 16S rRNA gene-based large-scale structural profiling of the giant panda fecal microbiota. Forty-five captive individuals were sampled in spring, summer, and late autumn within 1 year. Significant intraindividual variations in the diversity and structure of gut microbiota across seasons were observed in this population, which were even greater than the variations between individuals. Compared with published data sets involving 124 gut microbiota profiles from 54 mammalian species, these giant pandas, together with 9 captive and 7 wild individuals investigated previously, showed extremely low gut microbiota diversity and an overall structure that diverged from those of nonpanda herbivores but converged with those of carnivorous and omnivorous bears. The giant panda did not harbor putative cellulose-degrading phylotypes such as *Ruminococcaceae* and *Bacteroides* bacteria that are typically enriched in other herbivores, but instead, its microbiota was dominated by *Escherichia*/*Shigella* and *Streptococcus* bacteria. Members of the class *Clostridia* were common and abundant in the giant panda gut microbiota, but most of the members present were absent in other herbivores and were not phylogenetically related with known cellulolytic lineages. Therefore, the giant panda appears not to have evolved a gut microbiota compatible with its newly adopted diet, which may adversely influence the coevolutionary fitness of this herbivore.

RESEARCH ARTICLE

*Xue, mBio 6:e00022-15, 2015*

The Bamboo-Eating Giant Panda Harbors a Carnivore-Like Gut Microbiota



The good news…

They have adapted

ANIMAL PHYSIOLOGY

*Nie, Science 349:171, 2015*

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

Yonggang Nie,[1*] John R. Speakman,[2,3*] Qi Wu,[1*] Chenglin Zhang,[4] Yibo Hu,[1] Maohua Xia,[4] Li Yan,[1] Catherine Hambly,[3] Lu Wang,[2] Wei Wei,[1] Jinguo Zhang,[4] Fuwen Wei[1]†

The carnivoran giant panda has a specialized bamboo diet, to which its alimentary tract is poorly adapted. Measurements of daily energy expenditure across five captive and three wild pandas averaged 5.2 megajoules (MJ)/day, only 37.7% 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 vital organs and low physical activity. In addition, circulating levels of thyroid hormones thyroxine ($T_4$) and triiodothyronine ($T_3$) averaged 46.9 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.

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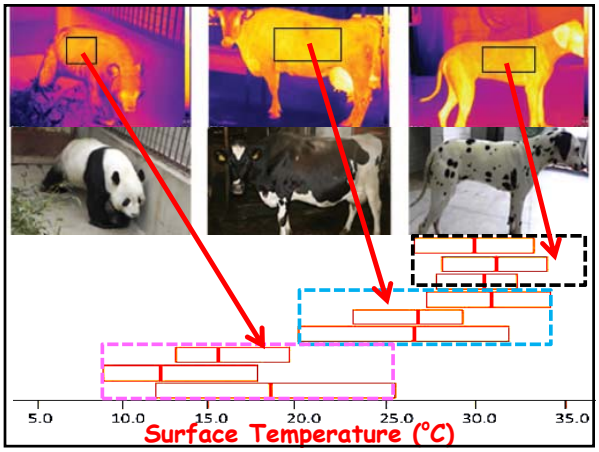
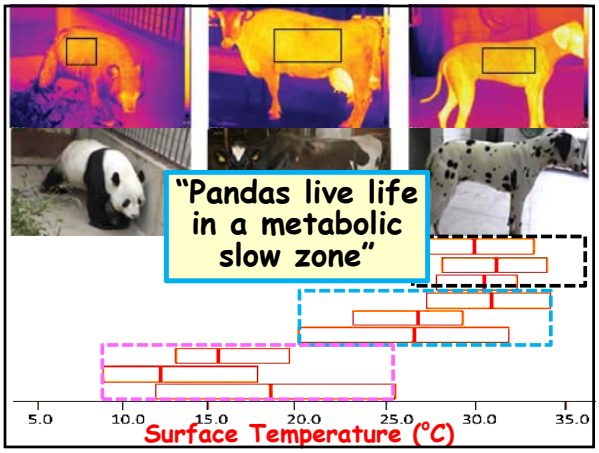
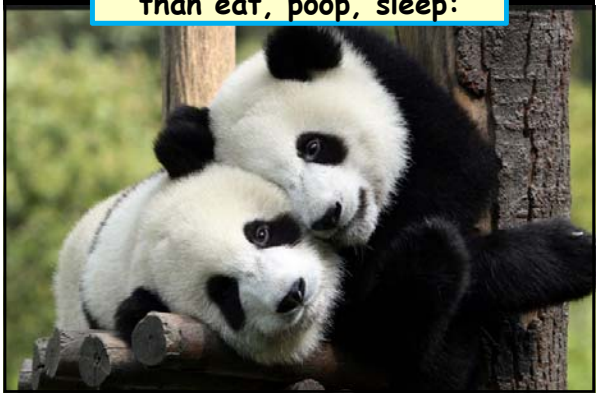
They achieve this by:
- reduced size of liver, brain, etc.
- low physical activity
- low levels of thyroid hormones



However, they do more than eat, poop, sleep:



The Washington Post

Local

Sun August 23, 2015

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

Smithsonian National Zoological Park Conservation Biology Institute | Friends of the National Zoo

Giant Pandas at the Smithsonian's National Zoo


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

NASPGHAN 2015

*Annual Meeting & Postgraduate Course*

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

NASPGHAN 2015

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**"NASPYS"**

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"Article of the Year"

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NATIONWIDE CHILDREN'S

*When your child needs a hospital, everything matters.*

PediatricsOnline | SEPTEMBER 2015

*E-newsletter for physicians and pediatric professionals*

**Infection's Link to Functional GI Disorders**

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

***Pensabene, J Pediatrics 166:903, 2015***

**Postinfectious Functional Gastrointestinal Disorders in Children: A Multicenter Prospective Study**

Licia Pensabene, MD, PhD[1], Valentina Talarico, MD[1], Daniela Concolino, MD[1], Domenico Ciliberto, MD[2], Angelo Campanozzi, MD[3], Teresa Gentile, MD[4], Vincenzo Rutigliano, MD[5], Silvia Salvatore, MD[6], Annamaria Staiano, MD[7], and Carlo Di Lorenzo, MD[8], 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 etiology.

**Study design** This was a prospective cohort multicenter study. Children 4-17 years of age presenting with acute diarrhea who tested positive for an enteric infection were recruited within 1 month from the episode and matched with control subjects of similar age and sex. Symptoms were evaluated with a validated questionnaire for FGIDs at the time of enrollment in the study and after 3 and 6 months.

**Results** A total of 64 patients (36 boys; median age 5.3 years; age range 4.1-14.1 years) were recruited, 32 subjects in each arm. Infections included rotavirus (56.8%), salmonella (30%), adenovirus (6.6%), norovirus (3.3%), and *Giardia lamblia* (3.3%). FGIDs were significantly more common in exposed patients compared with controls within 1 month from acute diarrhea (40.6% vs 12.5% [$P = .02$, relative risk (RR) = 1.9]), 3 months (53% vs 15.6% [$P = .003$, RR = 2.2]), and 6 months (46.8% vs 15.6% [$P = .01$, RR = 1.9]) later. No correlation was found between different etiologies, age, or sex, and any type of FGIDs. Among exposed children, abdominal pain–related FGIDs were significantly more frequent compared with controls after 6 months from infection ($P = .04$, RR = 1.7).

**Conclusion** 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;166:903-7*).

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

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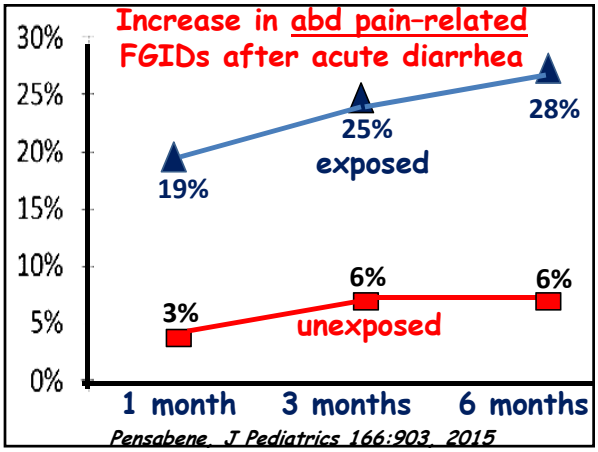


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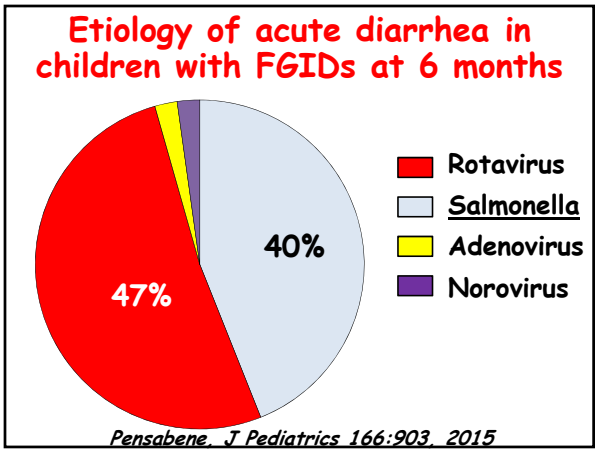


*Pensabene, J Pediatrics 166:903, 2015*

Gastroenterology 2014;147:69–77

CLINICAL—ALIMENTARY TRACT

## Salmonella Gastroenteritis During Childhood Is a Risk Factor for Irritable Bowel Syndrome in Adulthood

Antonio M. Morselli-Labate, Alexandro Paccapelo, Giovanni Di Nardo, Rosanna F. Cogliandro, Roberto De Giorgio, Roberto Corinaldesi, and Giovanni Barbara

*Cremon, Gastroenterology 147:69, 2014*

See editorial on page 18.

**BACKGROUND & AIMS:** Acute infectious gastroenteritis increases the risk for irritable bowel syndrome (IBS) and functional dyspepsia (FD). Children are particularly vulnerable to gastroenteritis because of the immaturity of their ... barrier, enteric nervous system, and ... pathogens. We investi... early life increa... hood. **METHODS:** ... culture-proven fo... involved 1811 pa... Clinical data were ... cohort study was d... long-term effects were assessed by mailing a questionnaire to 757 subjects 16 years after the outbreak (when all of the children were adults). We randomly selected a cohort of 250 adults exposed to *Salmonella* as chil-

...not just 6 months

reduced quality of life and high social costs.[1,2] The etiology of functional gastrointestinal disorders is not completely understood, resulting in unsatisfactory management.[1,3]

The mean number of annual ... of infectious gastroenteritis per ... proximately 3, with ... than 70 years ... ence of long- ... ysentery for ... *-dysenteric* ... gastroenteritis (eg, in- ... *Salmonella*, *Shigella*, *Campylobacter*, or ... Represents the strongest known risk factor for the development of IBS, which occurs in 3.7%–36.2% of exposed individuals[5,7] and accounts for 6%–17% of all IBS cases.[8] FD after gastroenteritis has also been reported but remains a poorly defined condition.[9,10] Limited information is available on the long-term outcomes of post-infectious IBS and post-infectious FD.[11–14] The Walkerton Health

Gastroenterology 2014;147:69–77

CLINICAL—ALIMENTARY TRACT

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- 1811 children-foodborne Salmonella F/U 16 years later:
  - 37% IBS (23% controls)
  - odds ratio for IBS in exposed = 1.9

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CLINICAL—ALIMENTARY TRACT

Salmonella Gastroenteritis During Childhood Is a Risk Factor for Irritable Bowel Syndrome in Adulthood

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*Cremon, Gastroenter... 4*

See editori...

"...preventive measures are needed to reduce the risk for IBS as adults"

- 181... Salmonella F... 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 SEPT. 4, 2015

...not just IBS!

lot of beef. It's also a lot of [illegible] than two billion po[illegible] harbor dangerous bacteria. T[illegible] after serious outbreaks of illness like the Jack in the Box case in 1993, when 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.

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

NASPGHAN 2015

*Annual Meeting & Postgraduate Course*

**"NASPYS"**

**Potential Advocacy Issue of the Year**

Food Safety (?) System

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

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AND CDC food safety

Updates on activities, events, and good-to-know info.

May 14, 2015 | Special Edition: Annual Food Safety Reports from CDC

**May 14, 2015**

## 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 germs 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 is still work to be done. Illness from six other infections monitored by FoodNet showed little or no recent improvements.

In 2014, Fo… s among residents of … anying materials.

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

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The New York Times

September 5, 2015

## *Cucumbers Recalled in Salmonella Outbreak*

The Centers for Disease Control and Prevention said cucumbers from Mexico were most likely the cause of a salmonella outbreak that began July 3 and has reached 27 states. Justin Sullivan/Getty Images

The Washington Post

October 6, 2015

To Your Health

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

By Lena H. Sun October 6 Follow @lylenasun

USA TODAY
A GANNETT COMPANY

NEWS SPORTS LIFE MONEY TECH TRAVEL OPINION 79° CROSSWORDS

## Peanut exec in salmonella case gets 28 years

Kevin McCoy, USA TODAY 5:39 a.m. EDT September 22, 2015

***National outbreak (2009):***

**-714 cases in 46 states**

**-9 deaths**


## How Safe Is Your Ground Beef?

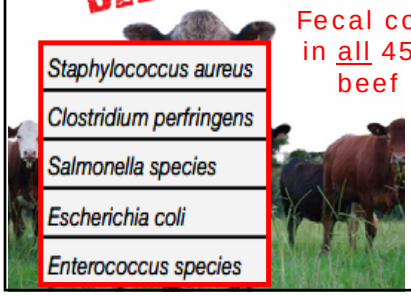
ConsumerReports
FOOD SAFETY & SUSTAINABILITY CENTER

BEEF REPORT

Fecal contamination in all 458 pounds of beef examined

ConsumerReports
FOOD SAFETY & SUSTAINABILITY CENTER

BEEF REPORT



Fecal contamination in all 458 pounds of beef examined

- *Staphylococcus aureus*
- *Clostridium perfringens*
- *Salmonella species*
- *Escherichia coli*
- *Enterococcus species*

## Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study

Melissa G Collier, Yury E Khudyakov, David Selvage, Meg Adams-Cameron, Erin Epson, Alicia Cronquist, Rachel H Jervis, Katherine Lamba, Akiko C Kimura, Rick Sowadsky, Rashida Hassan, Sarah Y Park, Eric Garza, Aleisha J Elliott, David S Rotstein, Jennifer Beal, Thomas Kuntz, Susan E Lance, Rebecca Dreisch, Matthew E Wise, Noele P Nelson, Anil Suryaprasad, Jan Drobeniuc, Scott D Holmberg, Fujie Xu, for the Hepatitis A Outbreak Investigation Team

*Collier, Lancet Infect Dis. 14:976, 2014*

**Summary**

**Background** In May, 2013, an outbreak of symptomatic hepatitis A virus infections occurred in the USA. Federal, state, and local public health officials investigated the cause of the outbreak a... investigated the source of the outbreak and assessed the public health r...

**Methods** We interviewed patients, obtained their shopping information... recovered from patients' serum and stool samples. We tested products f...

**Findings** Of 165 patients identified from ten states, 69 (42%) were admitted... and one needed a liver transplant; none died. Illness onset occurred from... patients was 47 years (IQR 35–58) and 91 (55%) were women. 153 patien... retailer A. 40 patients (24%) had product B in their freezers, and 113 (68... Hepatitis A virus genotype IB, uncommon in the Americas, was reco... hepatitis A virus illness. Pomegranate arils that were imported from Tu... identified in product B. No hepatitis A virus was detected in product B.

Bloomberg Business

## Listeria-Tainted Ice Cream


Bloomberg Business

## Listeria-Tainted Ice Cream Part of Broader Surge in Food Recalls

August 20, 2015 – 2:17 PM EDT

**3.7 million food items recalled in first half of 2015 (compared to 5.0 million for all of 2014)**

Stericycle ExpertSolutions said. That compares with 5.03 million in all of 2014, according to the firm's data, which was collected from the Food and Drug

Food Safety News

*Breaking news for everyone's consumption*

Home | Foodborne Illness Outbreaks | Food Recalls | Food Politics | Events | Subscribe | About

## Whole Foods Recalls Papillon Organic Roquefort Cheese Due to Listeria Risk

BY NEWS DESK | OCTOBER 8, 2015

**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 scale 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 whole, uncut wheel of the cheese.

The Papillon Organic Roquefort cheese product can be identified by the scale label that begins with PLU 029536. All sell-by dates are affected.

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


THE WALL STREET JOURNAL.

World U.S. Politics Economy Business Tech Markets Opinion Arts Life

## New FDA Rules Tighten Food Safety Requirements

Manufacturers will have to devise plans to prevent foodborne illness

**Sept. 10, 2015**


Foodsafety.gov

*Your Gateway to Federal Food Safety Information*

Home | Recalls & Alerts | Keep Food Safe | Who's at Risk | Food Poisoning

## 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**

The Washington Post

To Your Health

**Can the FDA actually prevent foodborne outbreaks instead of just reacting to them?**

**We're about to find out.**

Sept. 10, 2015

By Brady Dennis September 10 Follow @brady_dennis


## Bottom line = advocacy: Short-term & long term outcomes

**Vaccines**
**Food Safety**
***(Funding)***
**Food Prep**
**Food Handling**

NASPGHAN 2015

*Annual Meeting & Postgraduate Course*

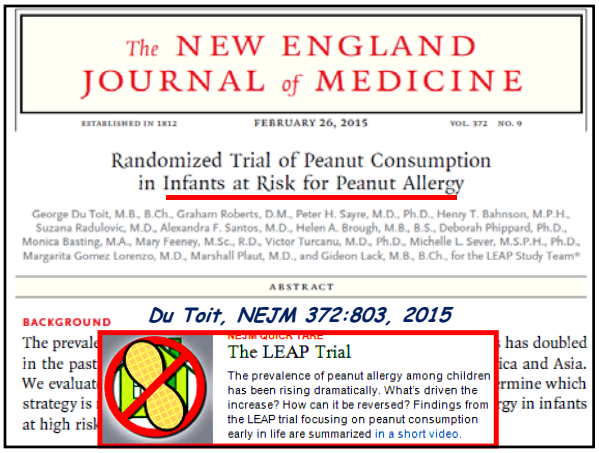
**"NASPYS"**

**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"


Du Toit, NEJM 372:803, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 26, 2015 VOL. 372 NO. 9

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

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

ABSTRACT

BACKGROUND

The prevalence of peanut allergy among children in Western countries has doubled in th... d Asia. We e... which strat... nfants at hi...

*Du Toit, NEJM 372:803, 2015*

**? strategy effective in preventing development of peanut allergy**

The NEW ENGLAND JOURNAL of MEDICINE

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ABSTRACT

BACKGROUND

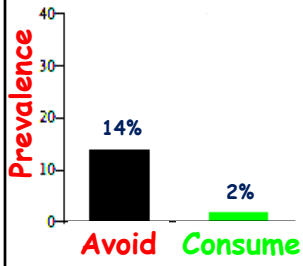
*Du Toit, NEJM 372:803, 2015*

The prevalence of peanut allergy among children in Western countries has doubled

- **Infants (4-10 mos) at high risk**
- **Consume/avoid peanuts until 60 mos**

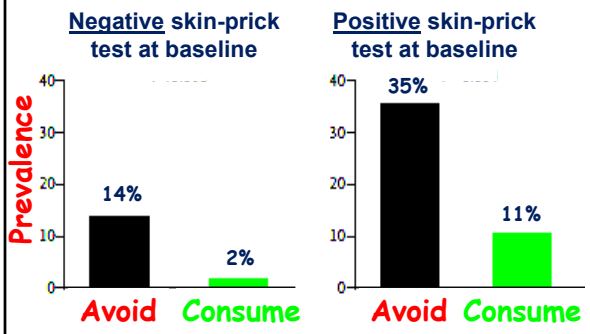
## Prevalence of Peanut Allergy

**Negative skin-prick test at baseline**




*Du Toit, NEJM 372:803, 2015*

## Prevalence of Peanut Allergy




*Du Toit, NEJM 372:803, 2015*

*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 butter to school. Some airlines no longer serve peanuts because of fear of anaphylaxis among passengers. These develop-

In 2000, largely in response to outcomes reported in infant feeding trials conducted in Europe and the United States, the American Acad-

**"Landmark Study"**
**"has the potential to transform how we approach food allergy prevention"**

has become the leading cause of anaphylaxis and death related to food allergy in the United States.[3]

viewing the published literature, the AAP retracted its recommendation, stating that there was

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

Primary contributors: David M. Fleischer, MD,[1] Scott Sicherer, MD,[2] Matthew Greenhawt, MD,[3] Dianne Campbell, MB BS, FRACP, PhD,[4] Edmond Chan, MD,[5] Antonella Muraro, MD, PhD,[6] Susanne Halken, MD,[6] Yitzhak Katz, MD,[7] Motohiro Ebisawa, MD, PhD,[8] Lawrence Eichenfield, MD,[9] Hugh Sampson, MD[10]

For the LEAP Study Team: Gideon Lack MB, BCh,[10] George Du Toit, MB, BCh,[4] Graham Roberts, DM,[4] Henry Bahnson, MPH,[11] Mary Feeney, MSc, RD[10]

**"…Infants at high risk for peanut allergy should start a peanut-based diet by age 4-11 months"**

*Fleischer, Pediatrics 136:600, 2015*

# What's Hot?

## TODAY




*Marild, Am J Gastroenterol (online) 8 October 2015*

### Infections and Risk of Celiac Disease in Childhood: A Prospective Nationwide Cohort Study

Karl Mårild, MD, PhD[1,2], Christian R. Kahrs, MD[1,3], German Tapia, PhD[1], Lars C. Stene, PhD[1] and Ketil Størdal, MD, PhD[1,3]

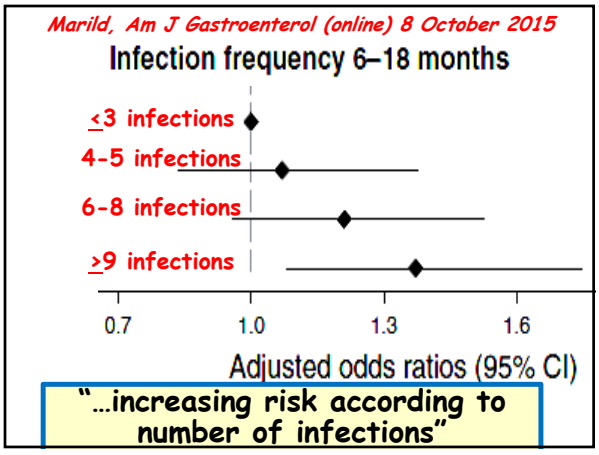
OBJECTIVES: Studies on early life infections and risk of later celiac disease (CD) are inconsistent but have mostly been limited to retrospective designs, inpatient data, or insufficient statistical power. We aimed to test whether early life infections are associated with increased risk of later CD using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

METHODS: This study, based on the Norwegian Mother and Child Cohort Study, includes prospective, repeated assessments of parent-reported infectious disease data up to 18 months of age for 72,921 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 (aOR).

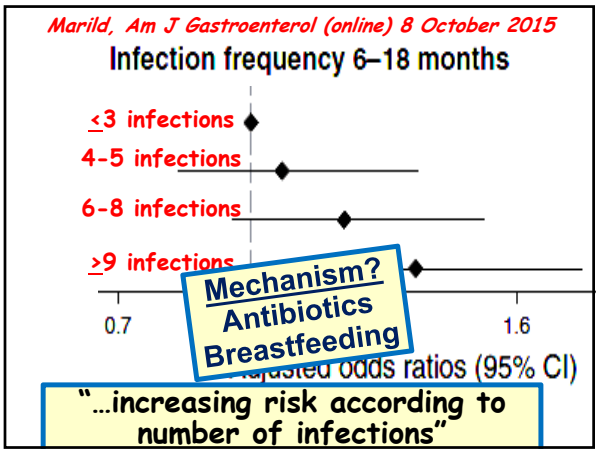
**"…high infection frequency in first 18 mos = increased risk of later CD"**

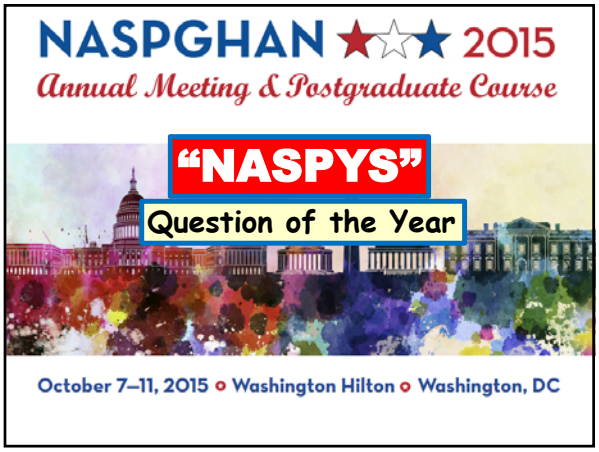
follows: upper respiratory tract infections: 1.03 (95% CI=1.02–1.05); lower respiratory tract infections: 1.12 (95% CI=1.01–1.23); and gastroenteritis: 1.05 (95% CI=0.99–1.11). Additional adjustments for maternal CD, education level, smoking, birth weight, prematurity, infant feeding practices, birth season, and antibiotic treatment yielded largely unchanged results.

*Marild, Am J Gastroenterol (online) 8 October 2015*




**"…increasing risk according to number of infections"**


Marild, Am J Gastroenterol (online) 8 October 2015
Infection frequency 6–18 months
<3 infections
4-5 infections
6-8 infections
>9 infections
0.7
1.6
Mechanism?
Antibiotics
Breastfeeding
"…increasing risk according to number of infections"


NASPGHAN 2015
Annual Meeting & Postgraduate Course
"NASPYS"
Question of the Year
October 7–11, 2015 • Washington Hilton • Washington, DC


Should we all go Gluten-Free???


Should we all go Gluten-Free???
Mandatory vs. Elective


Should we all go Gluten-Free???
Mandatory vs. Elective
Celiac Disease
NCGS


"you can't eat that!!!"
"I won't eat that!!!"
Mandatory vs. Elective

DAILY NEWS NEW YORK | NEWS | POLITICS

Majority of Americans think gluten-free diet will boost health: study 63%

100 million consume a GFD


GLUTEN FREE MUSEUM

GLUTEN FREE MUSEUM

## Why Do So Many People Think They Need Gluten-Free Foods?

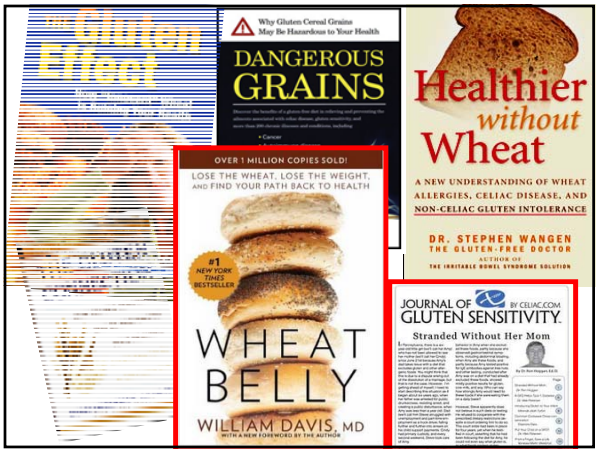
Some conditions are overdiagnosed, but some are underdiagnosed.

*By Darshak Sanghavi*

## The Fad Factor of the GFD

Lady Gaga goes on gluten free diet

Updated: 2012-08-20 14:45



GOMER BLOG
Earth's Finest Medical News Site

# How to Become Gluten Intolerant

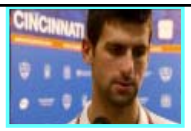
By **Doktor Schnabel** - August 17, 2015

Ever wonder how you can become gluten intolerant even if you don't actually have gluten intolerance or Celiac disease? We have found a video that describes how you can become gluten intolerant with some simple condescending 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 rave. 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."


Monday, May 16, 2011 As of 12:00 AM New York 79°|6

THE WALL STREET JOURNAL. | TENNIS




TENNIS | MAY 16, 2011

# The Diet That Shook Up Tennis?

*Starch Madness: Novak Djokovic's Domination of the Sport Has Coincided With His Gluten-Free Turn*

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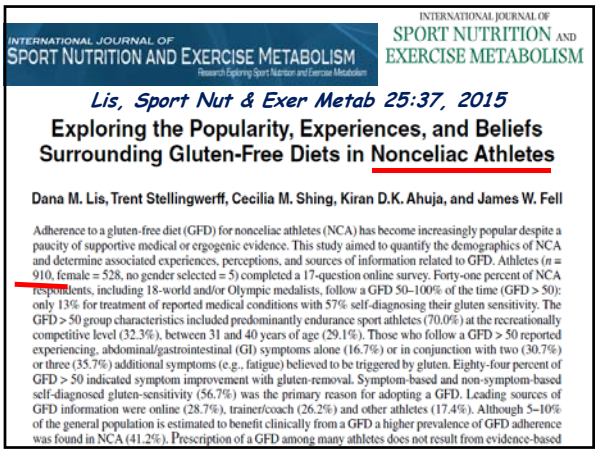

INTERNATIONAL JOURNAL OF SPORT NUTRITION AND EXERCISE METABOLISM

*Lis, Sport Nut & Exer Metab 25:37, 2015*

**Exploring the Popularity, Experiences, and Beliefs Surrounding Gluten-Free Diets in Nonceliac Athletes**

Dana M. Lis, Trent Stellingwerff, Cecilia M. Shing, Kiran 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 ergogenic evidence. This study aimed to quantify the demographics of NCA and determine associated experiences, perceptions, and sources of information related to GFD. Athletes ($n$ = 910, female = 528, no gender selected = 5) completed a 17-question online survey. Forty-one percent of NCA respondents, including 18-world and/or Olympic medalists, follow a GFD 50–100% of the time (GFD > 50): only 13% for treatment of reported medical conditions with 57% self-diagnosing their gluten sensitivity. The GFD > 50 group characteristics included predominantly endurance sport athletes (70.0%) at the recreationally competitive level (32.3%), between 31 and 40 years of age (29.1%). Those who follow a GFD > 50 reported experiencing, abdominal/gastrointestinal (GI) symptoms alone (16.7%) or in conjunction with two (30.7%) or three (35.7%) additional symptoms (e.g., fatigue) believed to be triggered by gluten. Eighty-four percent of GFD > 50 indicated symptom improvement with gluten-removal. Symptom-based and non-symptom-based self-diagnosed gluten-sensitivity (56.7%) was the primary reason for adopting a GFD. Leading sources of GFD information were online (28.7%), trainer/coach (26.2%) and other athletes (17.4%). Although 5–10% of the general population is estimated to benefit clinically from a GFD a higher prevalence of GFD adherence was found in NCA (41.2%). Prescription of a GFD among many athletes does not result from evidence-based

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**41% (including 18 World and/or Olympic medalists) follow a GFD**

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MEDICINE & SCIENCE IN SPORTS & EXERCISE®

Official Journal of the American College of Sports Medicine

AMERICAN COLLEGE of SPORTS MEDICINE www.acsm.org

No Effects of a Short-Term Gluten-free Diet on Performance in Nonceliac Athletes.

Lis, Dana; Stellingwerff, Trent; Kitic, Cecilia M.; Ahuja, Kiran DK; 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, intestinal injury, and inflammatory responses in non-celiac athletes.

*Lis, Med & Science in Sport & Exer (in press) 2015*

Well

The New York Times

## When Gluten Sensitivity Isn't Celiac Disease

By JANE E. BRODY OCTOBER 6, 2014 12:03 PM 234 Comments

## Nonceliac Gluten Sensitivity

Alessio Fasano[1] Anna Sapone[1,2] Victor Zevallos[3] Detlef Schuppan[1,3]


*Fasano, Gastroenterology 148:1195, 2015*

During the past decade there has been an impressive increase in popularity of the gluten-free diet (GFD)—now the most trendy alimentary habit in the United States and other countries. According to recent surveys, as many as 100 million Americans will consume gluten-free products within a year. Operating under the concept that the GFD 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 can be processed into many foods, such as breads, pasta, pizza, bulgur, couscous, and drinks such as beer. Furthermore, the functional properties of gluten proteins have led to their addition to many foods and cosmetics.

The same characteristics that make gluten so unique and desirable for human consumption also lead to diseases: the best known, wheat allergy and celiac disease, are mediated by the adaptive immune system [Figure 1]. Each disorder is

## 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


## Clinical Spectrum: Self-reported symptoms

## 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?


## Relationship: Gluten ↔ IBS?

## 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

Fernanda Cristofori, MD; Claudia Fontana, MD; Annamaria Magistà, MD; Teresa Capriati, MD; Flavia Indrio, MD; Stefania Castellaneta, MD; Luciano Cavallo, MD; Ruggiero Francavilla, MD, PhD

Editorial page 514
Supplemental co
jamapediatrics.co

**IMPORTANCE** 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, PARTICIPANTS** Six-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 (42.8% male; median age, 6.8 years) consecutively referred for recurrent abdominal pain by their primary care physicians without previous investigation were evaluated.

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

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Editorial page 514
Supplemental co

IMPORTANCE Recurrent abdominal pain is a prevalent health issue in childhood. Clinical

- **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?

## GLUTEN ↔ NCGS?

### Recall

- **Several Studies which suggested an association:**
- *Wahnschaffe, Clin Gastro Hepatol 5:844, 2007*
- *Biesiekierski, Amer J Gastro 106:508, 2011*
- *Vazquez-Roque, Gastro 144:903, 2013*

508 ORIGINAL CONTRIBUTIONS nature publishing group

COLON/SMALL BOWEL

### *Biesiekierski, Amer J Gastro 106:508, 2011*

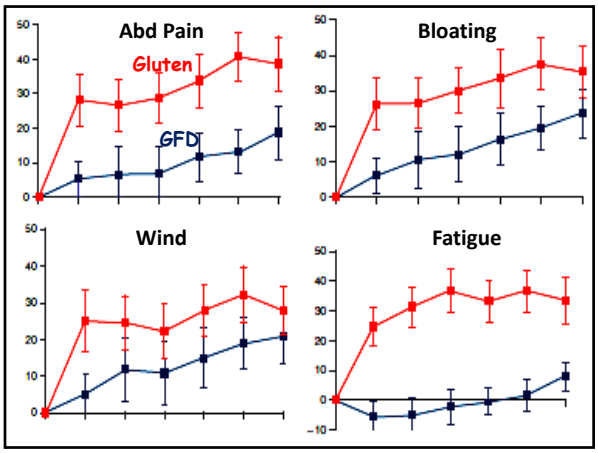
Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial

Jessica R. Biesiekierski, B Appl Sc[1], Evan D. Newnham, MD, FRACP[1], Peter M. Irving, MD, MRCP[1], Jacqueline S. Barrett, PhD, BSc, MND[1], Melissa Haines, MD[1], James D. Doecke, BSc, PhD[2], Susan J. Shepherd, B Appl Sci, PhD[1], Jane G. Muir, PhD, PGrad Dip(Dietetics)[1] and Peter R. Gibson, MD, FRACP[1]

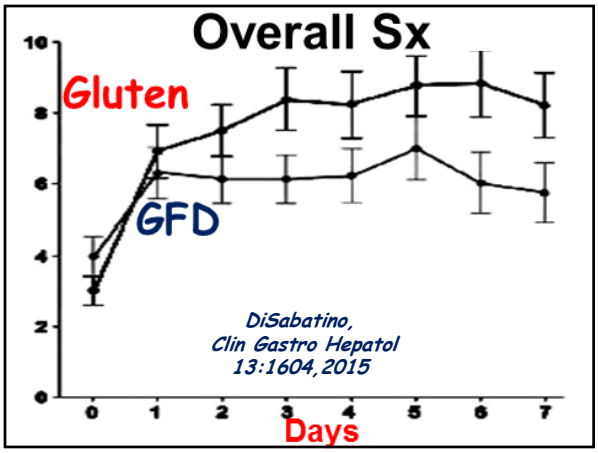
OBJECTIVES: **Despite increased prescription of a gluten-free diet for gastrointestinal symptoms in individuals who do not have celiac disease, there is minimal evidence that suggests that gluten is a trigger. The aims of this study were to determine whether gluten ingestion can induce symptoms in non-celiac individuals and to examine the mechanism.**

METHODS: **A double-blind, randomized, placebo-controlled rechallenge trial was undertaken in patients with irritable bowel syndrome in whom celiac disease was excluded and who were symptomatically controlled on a gluten-free diet. Participants received either gluten or placebo in the form of two bread slices plus one muffin per day with a gluten-free diet for up to 6 weeks. Symptoms were evaluated using a visual analog scale and markers of intestinal inflammation, injury, and immune activation were monitored.**

RESULTS: **A total of 34 patients (aged 29–59 years, 4 men) completed the study as per protocol. Overall, 56% had human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8. Adherence to diet and supplements was very high. Of 19 patients (68%) in the gluten group, 13 reported that symptoms were not adequately controlled compared with 6 of 15 (40%) on placebo ($P=0.0001$; generalized estimating equation). On a visual analog scale, patients were significantly worse with gluten within 1 week for overall symptoms ($P=0.047$), pain ($P=0.016$), bloating ($P=0.031$), satisfaction with stool consistency ($P=0.024$), and tiredness ($P=0.001$). Anti-gliadin antibodies were not induced. There were no significant changes in fecal lactoferrin, levels of celiac antibodies, highly sensitive C-reactive protein, or intestinal permeability. There were no differences in any end point in individuals with or without DQ2/DQ8.**


Abd Pain
Gluten
GFD
Bloating
Wind
Fatigue


Clinical Gastroenterology and H
Purified Gluten-4.4 gms/d
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 Caio,‡ Roberto De Giorgio,‡ Michele Di Stefano,* and Gino R. Corazza*
DiSabatino, Clin Gastro Hepatol 13:1604, 2015
BACKGROUND & AIMS:
There is debate over the existence of nonceliac gluten sensitivity (NCGS) intestinal and extra-intestinal symptoms in response to ingestion of gluten-containing foods by people without celiac disease or wheat allergy. We performed a randomized, double-blind, placebo-controlled, cross-over trial to determine the effects of administration of low doses of gluten to subjects with suspected NCGS.
METHODS:
We enrolled 61 adults without celiac disease or a wheat allergy who believed ingestion of gluten-containing food to be the cause of their intestinal and extraintestinal symptoms. Participants were assigned randomly to groups given either 4.375 g/day gluten or rice starch (placebo) for 1 week, each via gastrosoluble capsules. After a 1-week gluten-free diet, participants crossed over to the other group. The primary outcome was the change in overall (intestinal and extraintestinal) symptoms, determined by established scoring systems, between gluten and placebo intake. A secondary outcome was the change in individual symptom scores between gluten vs placebo.


Overall Sx
Gluten
GFD
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Clin Gastro Hepatol
13:1604, 2015
Days

SundayReview | OPINION

The Myth of Big, Bad Gluten

By MOISES VELASQUEZ-MANOFF JULY 4, 2015


SundayReview | OPINION

The Myth of Big, Bad Gluten

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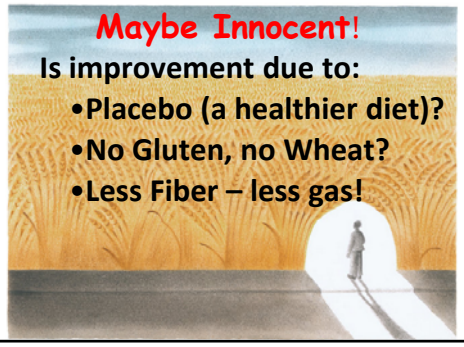


SundayReview | OPINION

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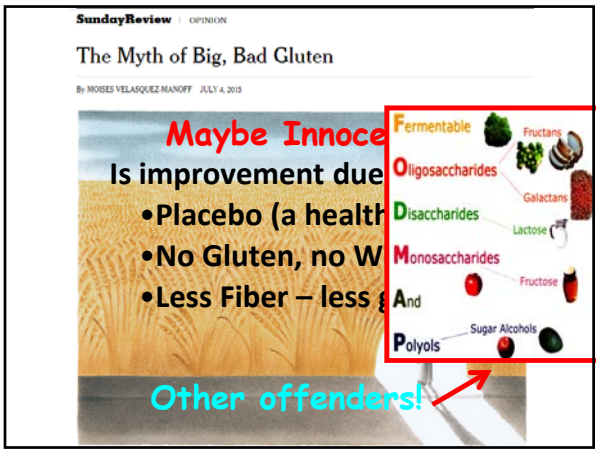
SundayReview | OPINION
The Myth of Big, Bad Gluten
By MOISES VELASQUEZ-MANOFF JULY 4, 2015
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And
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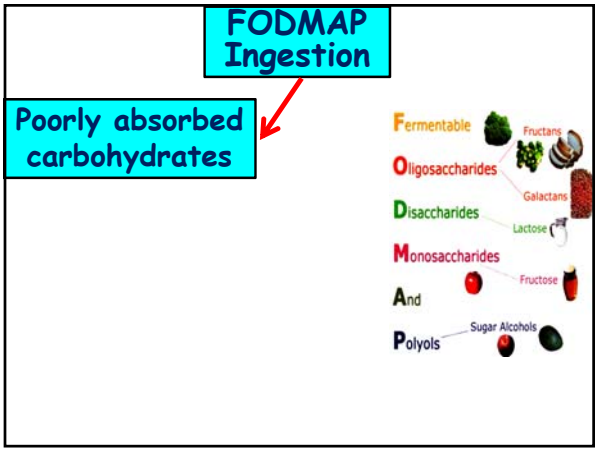
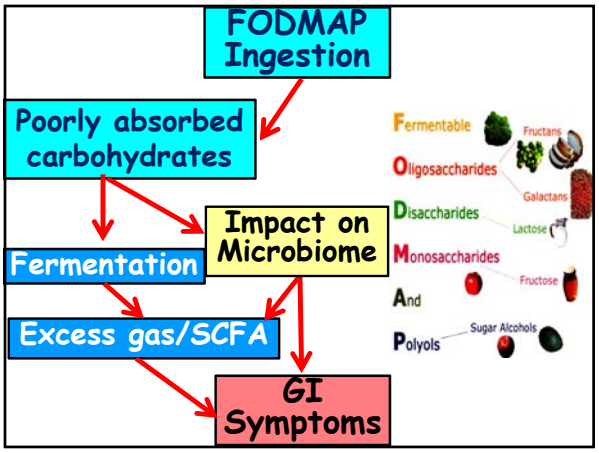
Sugar Alcohols


FODMAP Ingestion
Poorly absorbed carbohydrates
Fermentable
Oligosaccharides
Disaccharides
Monosaccharides
And
Polyols
Fructans
Galactans
Lactose
Fructose
Sugar Alcohols


FODMAP Ingestion
Poorly absorbed carbohydrates
Fermentation
Impact on Microbiome
Excess gas/SCFA
GI Symptoms
Fermentable
Oligosaccharides
Disaccharides
Monosaccharides
And
Polyols
Fructans
Galactans
Lactose
Fructose
Sugar Alcohols

AP&T Alimentary Pharmacology and Therapeutics

## Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome

B. P. Chumpitazi*, J. L. Cope†,§, E. B. Hollister†,§, C. M. Tsai*, A. R. McMeans†, R. A. Luna†,§, J. Versalovic†,§ & R. J. Shulman*,†

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

Backg
A low
(FOD
within

**a low FODMAP diet decreases abdominal pain frequency in IBS**

olyols
(IBS)

Aim

To determine the efficacy of a low FODMAP diet in childhood IBS and whether gut microbial composition and/or metabolic capacity are associated with its efficacy.

---

GASTROENTEROLOGY 2013;145:320–328

*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

JESSICA R. BIESIEKIERSKI,[1,2] SIMONE L. PETERS,[2] EVAN D. NEWNHAM,[1] OURANIA ROSELLA,[2] JANE G. MUIR,[2] and PETER R. GIBSON[2]

[1]Department of Gastroenterology, Eastern Health Clinical School, Monash University, Box Hill, Victoria, Australia and [2]Department of Gastroenterology, Central Clinical School, Monash University, The Alfred Hospital, Melbourne, Victoria, Australia

CLINICAL AT

Podcast interview: www.gastro.org/gastropodcast. Also available on iTunes. See editorial on page 276.

**BACKGROUND & AIMS:** Patients with non-celiac gluten sensitivity (NCGS) do not have celiac disease but their symptoms improve when they are placed on gluten-free diets. We investigated the specific effects of gluten after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates (fermentable, oligo-, di-, monosaccharides, and polyols [FODMAPs]) in subjects believed to have NCGS. **METHODS:** We performed a double-blind cross-over trial of 37 subjects (aged 24–61 y, 6 men) with NCGS and irritable bowel syndrome (based on Rome III criteria), but not celiac disease. Participants were randomly assigned to groups given a 2-week diet of reduced FODMAPs, and were then placed on high-gluten (16 g gluten/d), low-gluten (2 g gluten/d and 14 g whey protein/d), or control (16 g

gluten-containing products continues to increase worldwide.[2] The clinical entity of non-celiac gluten sensitivity (NCGS) has been defined as those without celiac disease but whose gastrointestinal symptoms improve on a gluten-free diet (GFD).[3,4] Since its original description in 1980,[5] reports of NCGS have not taken into account the presence of other components of wheat, particularly fructans, that might have been pathogenically responsible for the symptoms. The first evidence that gluten might specifically induce symptoms in patients with IBS derived from a randomized, placebo-controlled trial of a single dose of carbohydrate-deplete gluten in 36 patients remaining on their habitual GFD in parallel groups.[6] Although there is some evidence of the effects of gluten in animal models or cancer cell lines,[7–9] little else is known about this entity. For example, mechanisms have not been identified and dose dependence has not been demonstrated.

To further evaluate this concept of NCGS, the current

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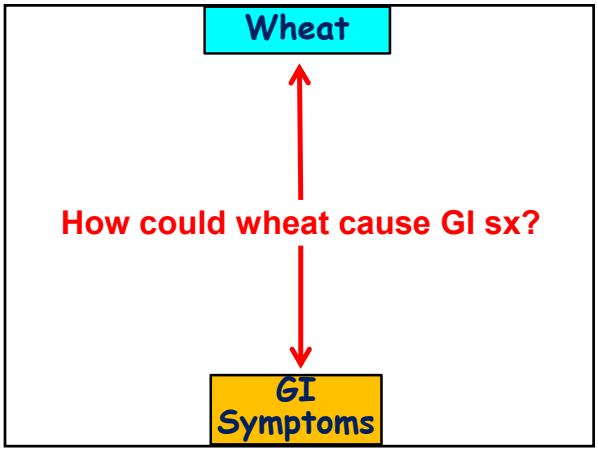
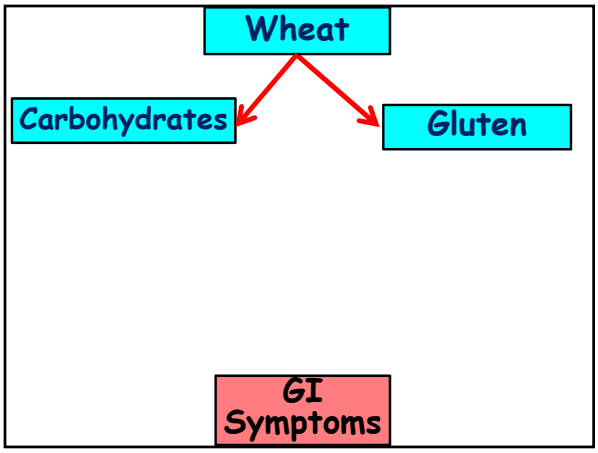
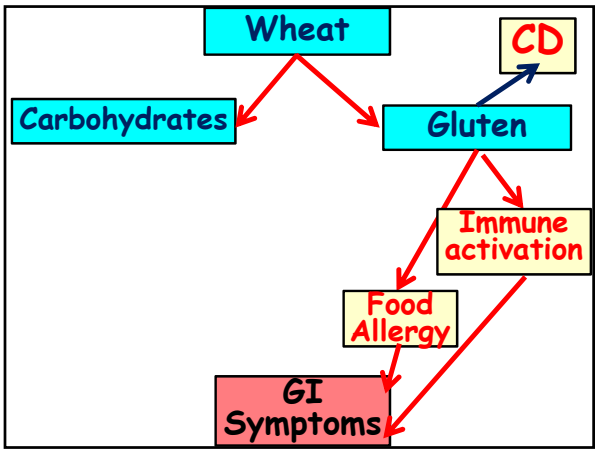
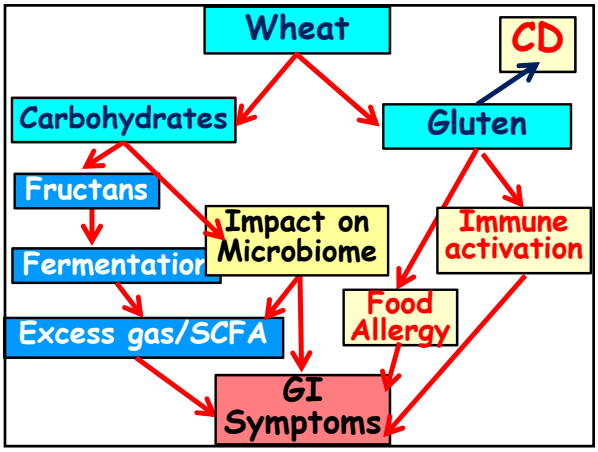
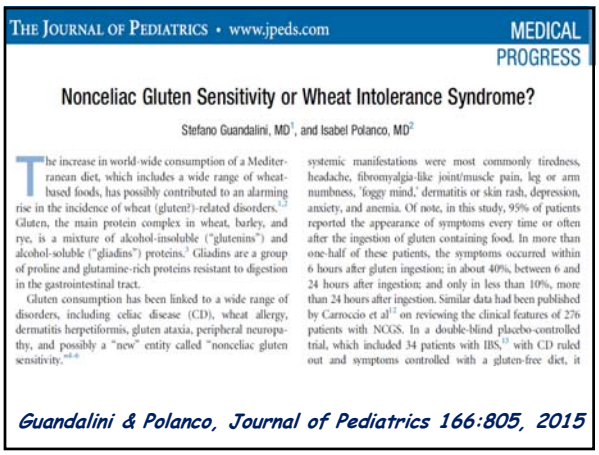
Is it the wheat??
GLUTEN FREE MUSEUM


Wheat
How could wheat cause GI sx?
GI Symptoms


Wheat
Carbohydrates
Gluten
GI Symptoms



THE JOURNAL OF PEDIATRICS • www.jpeds.com MEDICAL PROGRESS

Nonceliac Gluten Sensitivity or Wheat Intolerance Syndrome?

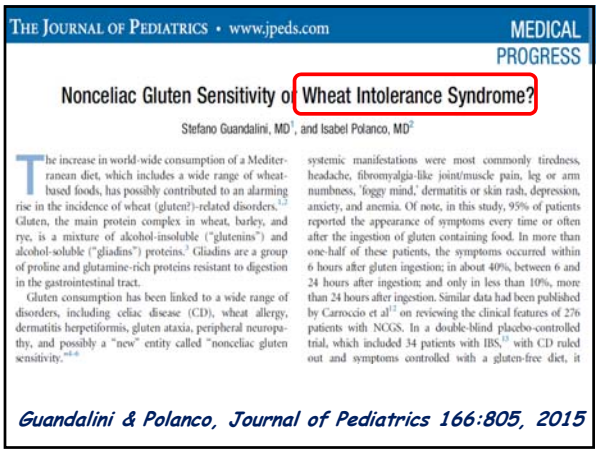
Stefano Guandalini, MD[1], and Isabel Polanco, MD[2]

The increase in world-wide consumption of a Mediterranean diet, which includes a wide range of wheat-based foods, has possibly contributed to an alarming rise in the incidence of wheat (gluten?)-related disorders.[1,2] Gluten, the main protein complex in wheat, barley, and rye, is a mixture of alcohol-insoluble ("glutenins") and alcohol-soluble ("gliadins") proteins.[3] Gliadins are a group of proline and glutamine-rich proteins 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 ataxia, peripheral neuropathy, and possibly a "new" entity called "nonceliac gluten sensitivity."[4-6]

systemic manifestations were most commonly tiredness, headache, fibromyalgia-like joint/muscle pain, leg or arm numbness, 'foggy mind,' dermatitis or skin rash, depression, anxiety, and anemia. Of note, in this study, 95% of patients reported the appearance of symptoms every time or often after the ingestion of gluten containing food. In more than one-half of these patients, the symptoms occurred within 6 hours after gluten ingestion; in about 40%, between 6 and 24 hours after ingestion; and only in less than 10%, more than 24 hours after ingestion. Similar data had been published by Carroccio et al[12] on reviewing the clinical features of 276 patients with NCGS. In a double-blind placebo-controlled trial, which included 34 patients with IBS,[13] with CD ruled out and symptoms controlled with a gluten-free diet, it

*Guandalini & Polanco, Journal of Pediatrics 166:805, 2015*



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*Guandalini & Polanco, Journal of Pediatrics 166:805, 2015*

## Wheat Intolerance Syndrome"

*Guandalini & Polanco, J Pediatr 166: 805, 2015*

- **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!


The Opinion Pages
ROOM *for* DEBATE

The New York Times

2-20-14

### Before Going Gluten-Free, Make Sure It's Necessary

Gluten is the spongy complex of proteins found in wheat, rye and barley, which puffs up when baked with yeast. Gluten-free foods are popular, and upwards of one-quarter of consumers apparently want them though only about 1 in 100 have celiac disease. Are we dealing with a crisis of hypochondria? Or is there a nuanced perspective?

To untangle this, it's critical to realize there are three different clinical problems worsened by gluten: celiac disease, wheat allergy and gluten intolerance. Celiac disease is an autoimmune problem where gluten hurts the small intestine, causing pain, diarrhea, severe rashes, and other problems. The disease was identified by a Dutch pediatrician who noted that some malnourished children recovered during a grain shortage in World War II. Celiac disease is properly diagnosed with blood tests and intestinal biopsies.

*When teens go gluten-free, they are much more likely to become overweight, and to eat less fiber, calcium and iron but consume more fat.*

## Suggested Approach

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!**

ENTEROLAB

SPECIALIZED LABORATORY TESTING FOR OPTIMAL INTESTINAL AND OVERALL HEALTH

**Test Panels**

Panel A1 + C1: Comprehensive Gluten/Antigenic Food Sensitivity Stool Panel

Panel B2 + C2: Comprehensive Gluten/Antigenic Vegetarian Food Sensitivity Stool Panel

Panel A1: Gluten/Antigenic Food Sensitivity Stool Panel Limited

Panel A2: Gluten/Antigenic Food Sensitivity Stool/Gene Panel

Panel B1: Gluten Sensitivity Stool Panel

Panel B2: Diet-Induced Inflammatory Bowel Panel Testing for Gluten Sensitivity, Oat Sensitivity, and Crohn's Disease

Panel B3: Gluten and Oat Sensitivity Stool Panel Complete

Panel C1: Antigenic Food Sensitivity Stool Panel

Panel C2: Vegetarian Antigenic Food Sensitivity Stool Panel

Panel C3: Antigenic Meat Sensitivity Stool Panel

Panel D1: Digestive Health Panel 1

**Individual Tests Also Contained in the Panels**

Gluten Sensitivity Stool Test (Fecal Anti-Gliadin IgA)

Oat Sensitivity Stool Test (Fecal Anti-Oat Protein IgA)

Milk Protein Sensitivity Stool Test (Fecal Anti-Casein IgA)

Fat Malabsorption Stool Test (Quantitative Fecal Fat Microscopy)

Egg Sensitivity Stool Test (Fecal Anti-Ovalbumin IgA)

Soy Sensitivity Stool Test (Fecal Anti-soy protein IgA)

Anti-Tissue Transglutaminase IgA Stool Test

Pancreatic Elastase Stool Test (Fecal Elastase)

Triple Parasite Stool Test (Enzyme Immunochromatography Test for *Giardia*, Amoeba, *Cryptosporidium*)

Gluten Sensitivity Gene Test (Molecular HLA-DQB1 analysis)


## 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:


Who Has the
Guts for Gluten?


Who Has the
Guts for Gluten?


NASPGHAN 2015
Annual Meeting & Postgraduate Course
"NASPYS"
Worst Article of the Year
October 7–11, 2015 • Washington Hilton • Washington, DC

IMPROBABLE RESEARCH

Research that makes people LAUGH and then THINK

Read the Magazine

September 15, 2015

## Winners of the Ig® Nobel Prize

**For achievements that first make people LAUGH then make them THINK**

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*Rubio, Food Microbiology, 38:303, 2014*
*Rubio, Meat Science, 96:937, 2014*

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Contents lists available at ScienceDirect

Meat Science

journal homepage: www.elsevier.com/locate/meatsci

MEAT SCIENCE

ELSEVIER

### Characterization of lactic acid bacteria isolated from infant faeces as potential probiotic starter cultures for fermented sausages

Raquel Rubio, Anna Jofré, Belén Martín, Teresa Aymerich, Margarita Garriga*

ABSTRACT

A total of 109 lactic acid bacteria isolated from infant faeces were identified by partial 16S rRNA, cpn60 and/or *pheS* sequencing. *Lactobacillus* was the most prevalent genus, representing 48% of the isolates followed by *Enterococcus* (38%). *Lactobacillus gasseri* (21%) and *Enterococcus faecalis* (38%) were the main species detected. A further selection of potential probiotic starter cultures for fermented sausages focused on *Lactobacillus* as the most technologically relevant genus in this type of product. Lactobacilli strains were evaluated for their ability to grow *in vitro* in the processing conditions of fermented sausages and for their functional and safety properties, including antagonistic activity against foodborne pathogens, survival from gastrointestinal tract conditions (acidity, bile and pancreatin), tyramine production, antibiotic susceptibility and aggregation capacity. The best strains according to the results obtained were *Lactobacillus casei/paracasei* CTC1677, *L. casei/paracasei* CTC1678, *Lactobacillus rhamnosus* CTC1679, *L. gasseri* CTC1700, *L. gasseri* CTC1704, *Lactobacillus fermentum* CTC1693. Those strains were further assayed as starter cultures in model sausages. *L. casei/paracasei* CTC1677, *L. casei/paracasei* CTC1678 and *L. rhamnosus* CTC1679 were able to lead the fermentation and dominate (levels *ca.* $10^8$ CFU/g) the endogenous lactic acid bacteria, confirming their suitability as probiotic starter cultures.

*Rubio, Meat Science, 96:937, 2014*

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**Bacteria isolated from infant diapers used to ferment meat "…make delicious sausages"**



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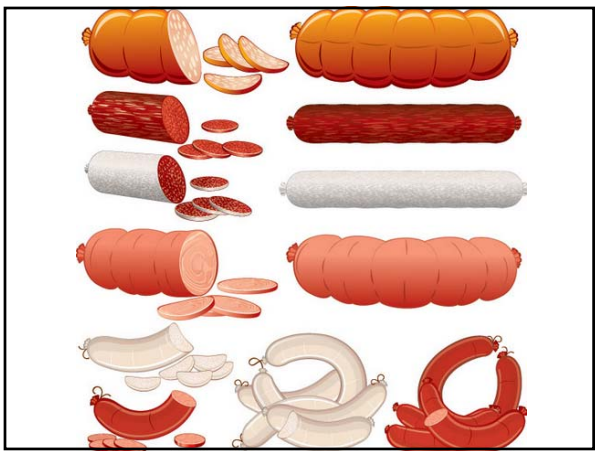
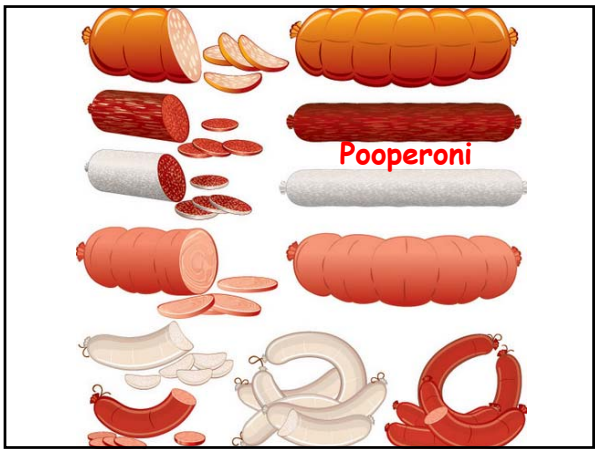
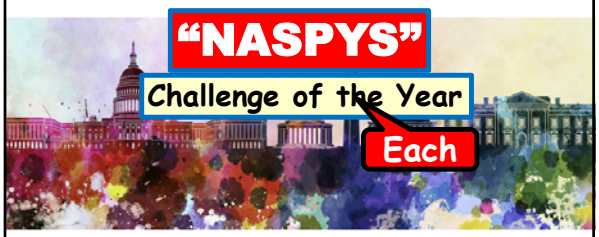





NASPGHAN ★☆★ 2015

*Annual Meeting & Postgraduate Course*

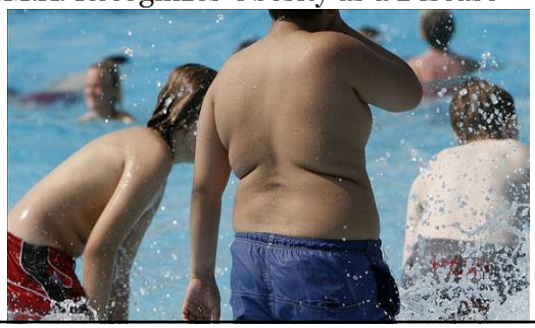



October 7–11, 2015 ○ Washington Hilton ○ Washington, DC

The New York Times **Business Day**

WORLD | U.S. | N.Y. / REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS

A.M.A. Recognizes Obesity as a Disease



The New York Times

**Business Day**

WORLD | U.S. | N.Y. / REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS

## A.M.A. Recognizes Obesity as a Disease

**NASH prevalence increased by 170% in registrants listed for liver transplant**

*Wong, Gastroenterology 148:547, 2014*



TRANSPLANT INTERNATIONAL

**Liver Transplantation for Nonalcoholic Steatohepatitis (NASH) in Young Patients**

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

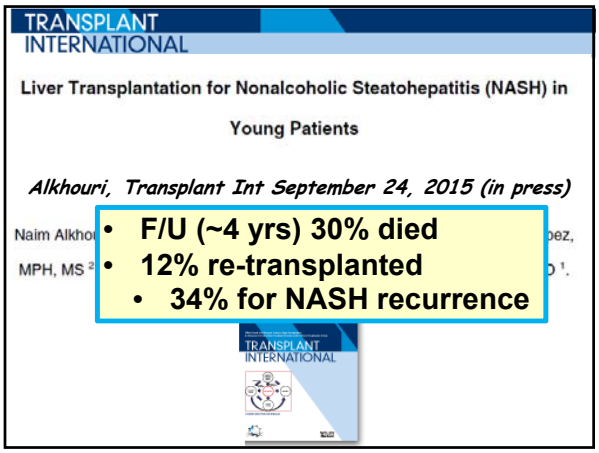
Naim Alkhouri, MD [1]; Ibrahim A Hanouneh, MD [1]; Nizar N Zein, MD [1]; Rocio Lopez, MPH, MS [2]; Dympna Kelly, MD [1]; Bijan Eghtesad, MD [1]; John J Fung, MD, PhD [1].

TRANSPLANT INTERNATIONAL

**Liver Transplantation for Nonalcoholic Steatohepatitis (NASH) in Young Patients**

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

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




## Challenges

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

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## Challenges

1. What is the Mechanism?
2. s?
3.

- **Most common default:**
  - **Diet**
  - **Sleep**
  - **Activity**
- **Rare = monogenic causes**

*Complex*

Treatment

## Challenges

1. What is the Mechanism?
2. s?
3.

- **Most common:**

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

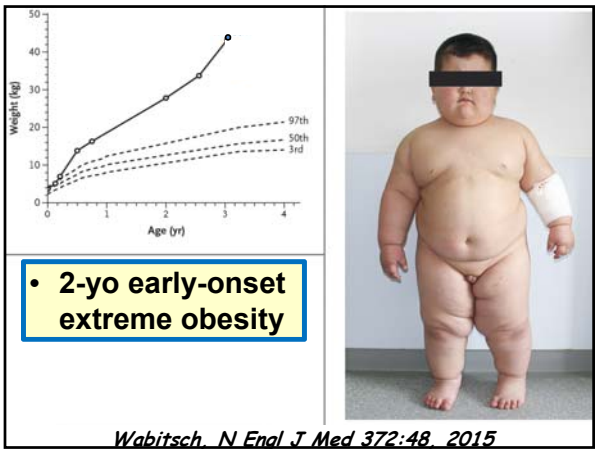
### Biologically Inactive Leptin and Early-Onset Extreme Obesity

Martin Wabitsch, M.D., Ph.D., Jan-Bernd Funcke, M.Sc., Belinda Lennerz, M.D., Ursula Kuhnle-Krahl, M.D., Georgia Lahr, Ph.D., Klaus-Michael Debatin, M.D., Petra Vatter, Ph.D., Peter Gierschik, M.D., Barbara Moepps, Ph.D., and Pamela Fischer-Posovszky, Ph.D.

*Wabitsch, NEJM 372:48, 2015*

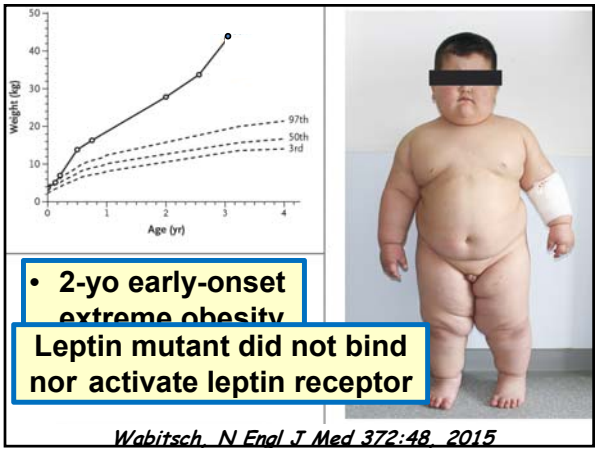
SUMMARY

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 (c.298G→T) in *LEP*, leading to a change from aspartic acid to tyrosine at amino acid position 100 (p.D100Y) 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 (metreleptin) rapidly normalized eating behavior and resulted in weight loss.




- 2-yo early-onset extreme obesity

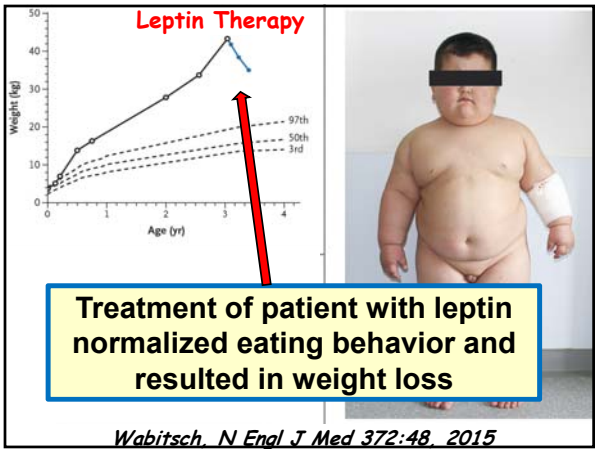
*Wabitsch. N Engl J Med 372:48. 2015*




- 2-yo early-onset extreme obesity

**Leptin mutant did not bind nor activate leptin receptor**

*Wabitsch. N Engl J Med 372:48. 2015*




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

*Wabitsch. N Engl J Med 372:48. 2015*

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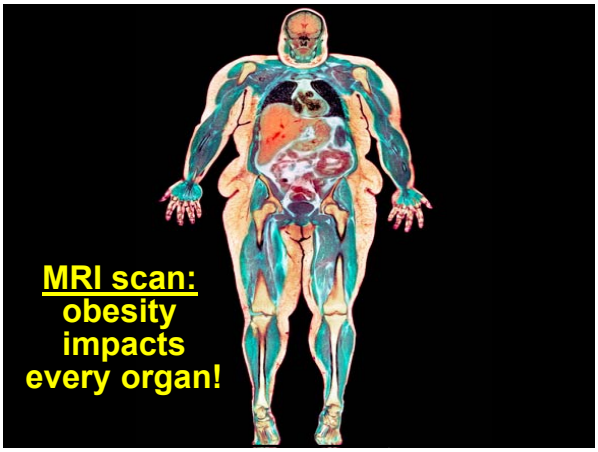
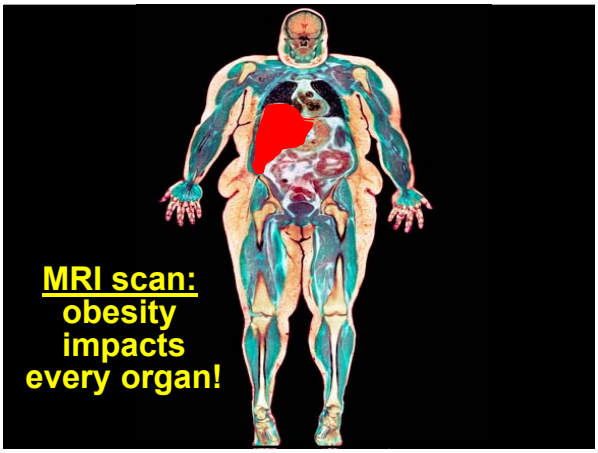


Gastroenterology 2015;149:623–634

# High Prevalence of Nonalcoholic Fatty Liver Disease in Adolescents Undergoing Bariatric Surgery

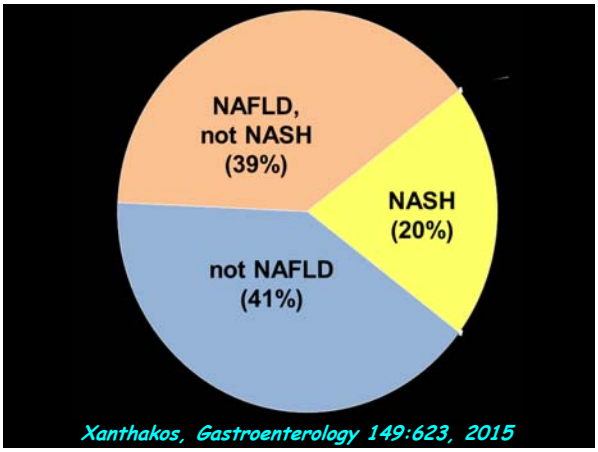
Stavra A. Xanthakos,[1] Todd M. Jenkins,[2] David E. Kleiner,[3] Tawny W. Boyce,[4] Reena Mourya,[1] Rebekah Karns,[5] Mary L. Brandt,[6] Carroll M. Harmon,[7] Michael A. Helmrath,[2] Marc P. Michalsky,[8] Anita P. Courcoulas,[9] Meg H. Zeller,[10] and Thomas H. Inge,[2] for the Teen-LABS Consortium

[1]Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio; [2]Division of Pediatric Surgery, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio; [3]Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; [4]University of New Mexico Cancer Center, Biostatistics Shared Resource, Albuquerque, New Mexico; [5]Division of Biomedical Informatics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio; [6]Division of Pediatric Surgery, Texas Children's Hospital, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas; [7]Division of Pediatric Surgery, Women & Children's Hospital of Buffalo, University of Buffalo School of Medicine and Biomedical Sciences, Buffalo, New York; [8]Department of Pediatric Surgery, The Ohio State University College of Medicine and Nationwide Children's Hospital, Columbus, Ohio; [9]Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and [10]Division of Behavioral Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

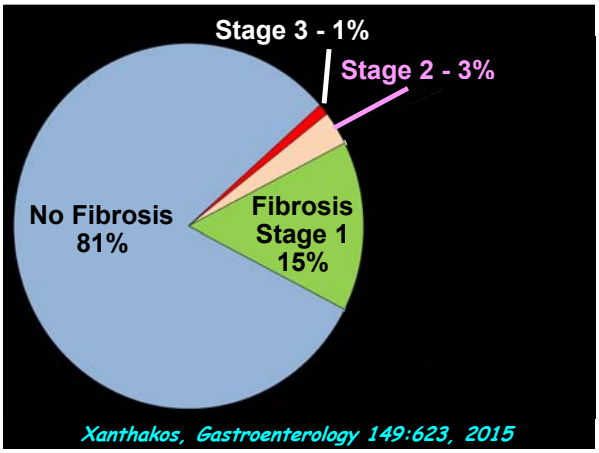
**BACKGROUND & AIMS:** Little is known about the prevalence of nonalcoholic fatty liver disease (NAFLD) among severely

*Keywords:* Pediatric; Severe Obesity; Microarray; Inflammation.

*Xanthakos, Gastroenterology 149:623, 2015*




*Xanthakos, Gastroenterology 149:623, 2015*

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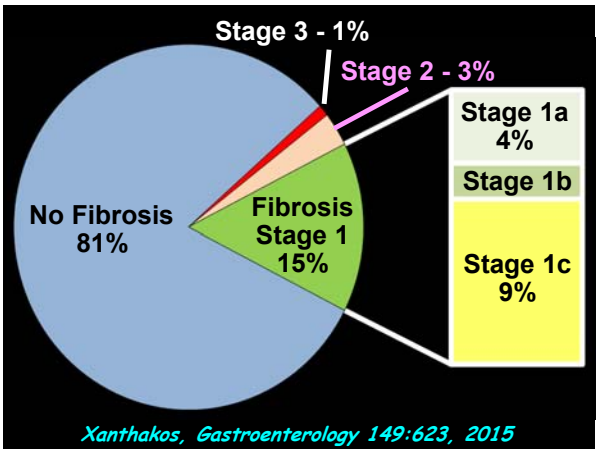
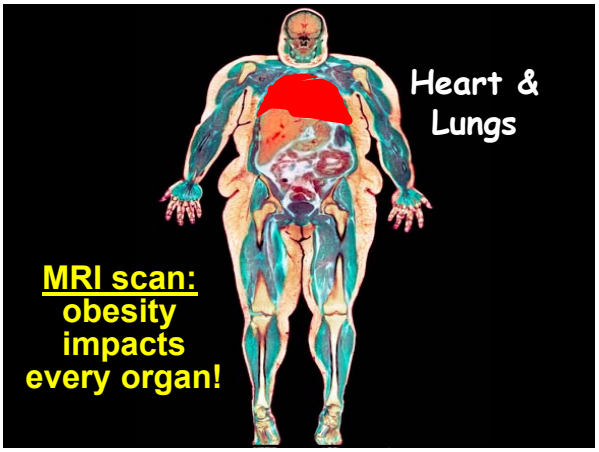
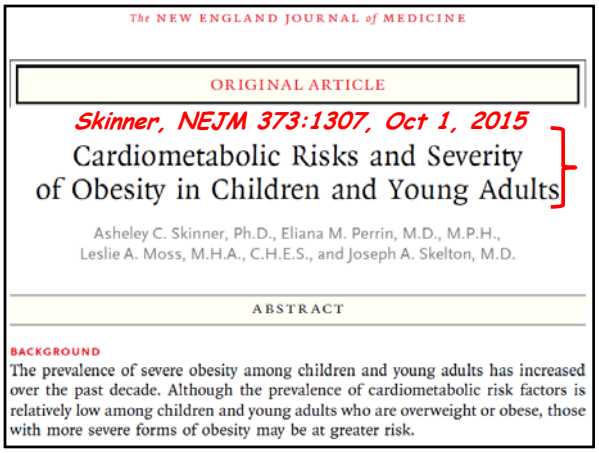


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Skinner, NEJM 373:1307, Oct 1, 2015

Cardiometabolic Risks and Severity of Obesity in Children and Young Adults

Asheley C. Skinner, Ph.D., Eliana M. Perrin, M.D., M.P.H., Leslie A. Moss, M.H.A., C.H.E.S., and Joseph A. Skelton, M.D.

ABSTRACT

BACKGROUND

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.

*Michalsky, JAMA Pediatr. 169:438, 2015*

Original Investigation

## Cardiovascular Risk Factors in Severely Obese Adolescents
## The Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) Study

Marc P. Michalsky, MD; Thomas H. Inge, MD, PhD; Mark Simmons, MEng; Todd M. Jenkins, PhD; Ralph Buncher, ScD; Michael Helmrath, MD; Mary L. Brandt, MD; Carroll M. Harmon, MD, PhD; Anita Courcoulas, MD; Michael Chen, MD; Mary Horlick, MD; Stephen R. Daniels, MD, PhD; Elaine M. Urbina, MD, MS; for the Teen-LABS Consortium

**IMPORTANCE** Severe obesity is increasingly common in the adolescent population but, as of yet, very little information exists regarding cardiovascular disease (CVD) risks in this group.

**OBJECTIVE** To assess the baseline prevalence and predictors of CVD risks among severely obese adolescents undergoing weight-loss surgery.

**DESIGN, SETTING, AND PARTICIPANTS** A prospective cohort study was conducted from February 28, 2007, to December 30, 2011, at the following 5 adolescent weight-loss surgery centers in the United States: Nationwide Children's Hospital in Columbus, Ohio; Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio; Texas Children's Hospital in Houston; University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania; and Children's Hospital

*Michalsky, JAMA Pediatr. 169:438, 2015*

Original Investigation

Cardiovascular Risk Factors in Severely Obese Adolescents
The Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) Study

**Baseline prevalence -**
**predictors of CVD (risk factor):**
- **fasting hyperinsulinemia (74%)**
- **elevated CRP (75%)**
- **dyslipidemia (50%)**
- **elevated BP (49%)**

University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania; and Children's Hospital

*Michalsky, JAMA Pediatr. 169:438, 2015*

Original Investigation

Cardiovascular Risk Factors in Severely Obese Adolescents
The Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) Study

**Cardiometabolic risk factors associated with NAFLD severity**
*Xanthakos, Gastroenterology 149:623, 2015*

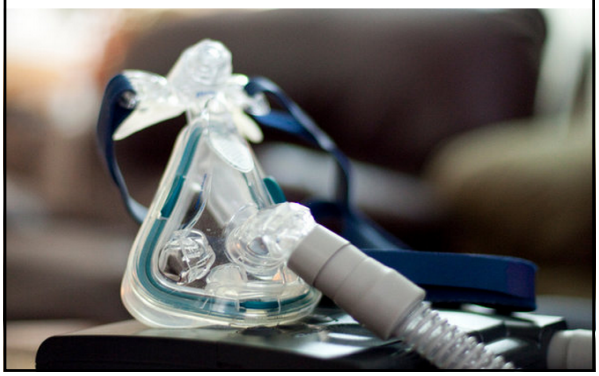
**CRP (75%)**
- **dyslipidemia (50%)**
- **elevated BP (49%)**

University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania; and Children's Hospital

ASK WELL

The New York Times

## Ask Well: Are Fatty Liver and Sleep Apnea Related?



ASK WELL

The New York Times

## Ask Well: Are Fatty Liver and Sleep Apnea Related?

**YES** - *Minville, CHEST 145:525, 2014*

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

*Sundaram, J Pediatr 164:699, 2014*

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

Shikha S. Sundaram, MD, MSCI[1], Ronald J. Sokol, MD[1], Kelley E. Capocelli, MD[2], Zhaoxing Pan, PhD[3], Jillian S. Sullivan, MD[1], Kristen Robbins[1], and Ann C. Halbower, MD[4]

**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).

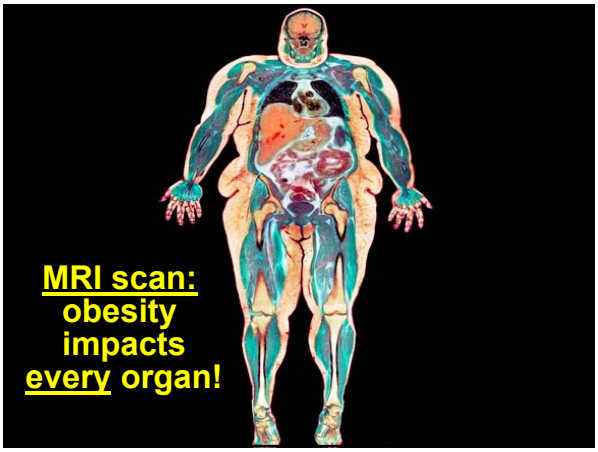
**Study design** Obese children aged 10-18 years with liver biopsy–proven NAFLD were enrolled. Demographic, clinical, and laboratory data were collected, polysomnography was performed, and liver histology was scored. Subjects were divided into those with OSA/hypoxemia and those without OSA/hypoxemia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

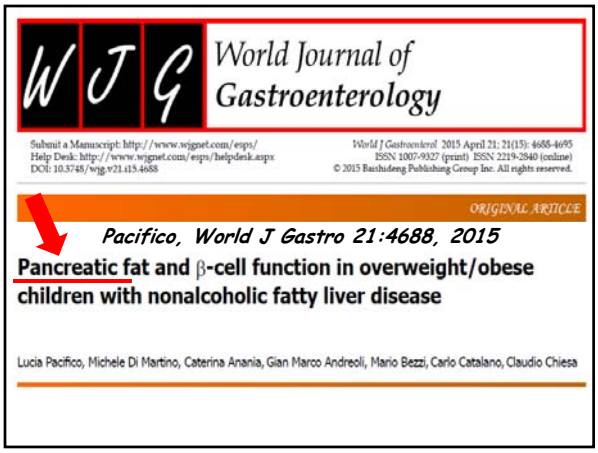
**Results** Of 25 subjects with NAFLD, OSA/hypoxemia was present in 15 (60%) (mean age, 12.8 ± 1.9 years; 68% male; 88% Hispanic; mean body mass index z-score, 2.3 ± 0.3). Subjects with and without OSA/hypoxemia had similar levels of serum aminotransferases, serum lipids, and inflammatory and insulin resistance markers. Although there were no differences between groups in the histological severity of steatosis, inflammation, ballooning degeneration, NAFLD activity score, or histological grade, subjects with OSA/hypoxemia had significantly more severe hepatic fibrosis. Moreover, oxygen saturation nadir during polysomnography was related to hepatic fibrosis stage ($r = -0.49$; $P = .01$) and aspartate aminotransferase level ($r = 0.42$; $P < .05$). Increasing percentage of time with oxygen saturation ≤90% was related to NAFLD inflammation grade ($r = 0.44$; $P = .03$), degree of hepatic steatosis ($r = -0.50$; $P = .01$), NAFLD activity score ($r = 0.42$; $P = .04$), aspartate aminotransferase level ($r = 0.56$; $P = .004$), and alanine aminotransferase level ($r = 0.44$; $P = .03$).

**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. (*J Pediatr 2014;164:699-706*).

# What's Hot?

## TODAY

FRIDAY, OCTOBER 9, 2015

POSTER SESSION II
12:00 PM - 2:00 PM
Columbia Exhibit Hall

Poster #336* *Poster of Distinction

**THE PREVALENCE OF TYPE 2 DIABETES AND PREDIABETES IN CHILDREN WITH NONALCOHOLIC FATTY LIVER DISEASE AND THEIR ASSOCIATION WITH NONALCOHOLIC STEATOHEPATITIS**

Kimberly P. Newton4, JIAYI HOU4, Nancy A. Crimmins1, Joel E. Lavine2, Sarah E. Barlow3, Stavra A. Xanthakos1, Jonathan Africa4, Cynthia Behling5, Michele Donithan6, Jeanne M. Clark6, Jeffrey B. Schwimmer4.

1Cincinnati Children's Hospital; 2Pediatrics, Columbia University; 3Texas Children's Hospital; 4University of California San Diego; 5Pathology, Sharp Medical Center; 6Johns Hopkins Bloomberg School of Public Health

**Objective:** Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children in North America. NAFLD is believed to be a risk factor for diabetes; however the prevalence rates and impact of type 2 diabetes in children with NAFLD are not well described. The study aims were to: 1) determine the p… sess diabetes and prediabetes

**Higher than expected based on obesity alone**

ORIGINAL ARTICLE

## Nonalcoholic fatty pancreas disease and Nonalcoholic fatty liver disease: more than ectopic fat

C. Della Corte*,[1], A. Mosca*,[1], F. Majo†, V. Lucidi†, N. Panera‡, E. Giglioni§, L. Monti¶, L. Stronati**, A. Alisi‡ and V. Nobili*

*Hepato-Metabolic Department, 'Bambino Gesù' Children's Hospital, IRCCS, †Cystic Fibrosis Unit, Pediatric Department, 'Bambino Gesù' Children's Hospital, IRCCS, ‡Liver Research Unit, 'Bambino Gesù' Children's Hospital, IRCCS, §Emergency Department, Bambino Gesù Children's Hospital, IRCCS, ¶Liver and Digestive Radiology Unit, Department of Imaging, Bambino Gesu' Children's Hospital, IRCCS, and **Institute of Biology, Molecular Medicine and Nanobiotechnology, CNR, Roma, Italy

*DellaCorte, Clin Endocrinol, in press, Oct 2015*

**Summary**

**Objective** The aim of this study was to evaluate the metabolic effects of fatty pancreas (nonalcoholic fatty pancreas disease – NAFPD) in a group of obese paediatric patients with nonalcoholic fatty liver disease (NAFLD).

**Methods** We included 121 consecutive children with echographic evidence of hepatic steatosis. All patients underwent to abdominal ultrasound to evaluate pancreatic echogenic pattern. We divided the patients into two groups on the basis of the presence of fatty pancreas. In all patients liver function tests, lipid and gluco-insulinemic profile were evaluated. A selected subset of patients (67) underwent to liver biopsy.

**Introduction**

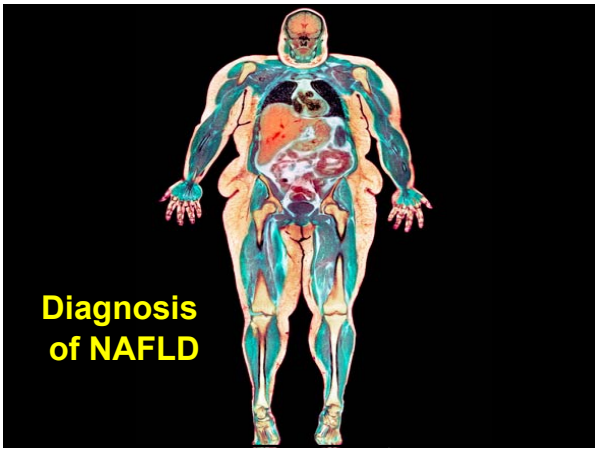
In the past 20 years, obesity has become epidemic in industrialized countries (USA, Europe, Australia), where more than 30% of children are obese, with serious adverse effects on public health.[1] It is demonstrated that childhood obesity causes several metabolic complications including type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), nonalcoholic fatty liver disease (NAFLD) and cardiovascular diseases (CVD).[2]

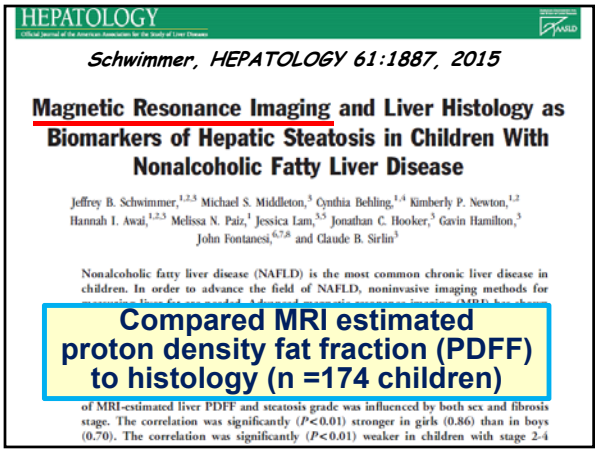
During the course of obesity, following the phases of hypertrophy and hyperplasia of adipocytes, to meet the demand of

## "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



HEPATOLOGY

Official Journal of the American Association for the Study of Liver Diseases

*Schwimmer, HEPATOLOGY 61:1887, 2015*

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

Jeffrey B. Schwimmer,[1,2,3] Michael S. Middleton,[3] Cynthia Behling,[1,4] Kimberly P. Newton,[1,2] Hannah I. Awai,[1,2,3] Melissa N. Paiz,[1] Jessica Lam,[3,5] Jonathan C. Hooker,[3] Gavin Hamilton,[3] John Fontanesi,[6,7,8] and Claude B. Sirlin[3]

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

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

of MRI-estimated liver PDFF and steatosis grade was influenced by both sex and fibrosis stage. The correlation was significantly ($P<0.01$) stronger in girls (0.86) than in boys (0.70). The correlation was significantly ($P<0.01$) weaker in children with stage 2-4

HEPATOLOGY

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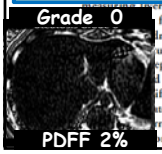
**Excellent correlation between PDFF & liver fat content (steatosis grade)**




for the quantitative assessment of hepatic steatosis but has not been validren. Therefore, this study was designed to evaluate the correlation and uracy of MRI-estimated liver proton density fat fraction (PDFF), a biopatic steatosis, compared to histologic steatosis grade in children. The l 174 children with a mean age of 14.0 years. Liver PDFF estimated by ificantly ($P<0.01$) correlated (0.725) with steatosis grade. The correlation ted liver PDFF and steatosis grade was influenced by both sex and fibrosis relation was significantly ($P<0.01$) stronger in girls (0.86) than in boys rrelation was significantly ($P<0.01$) weaker in children with stage 2-4

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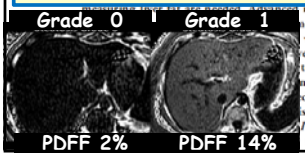


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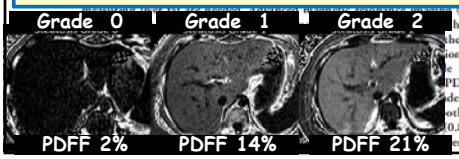


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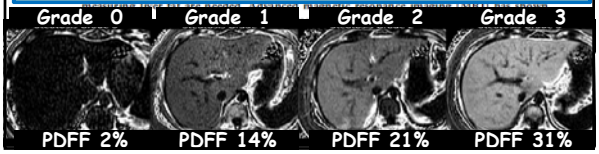


HEPATOLOGY

*Vos, HEPATOLOGY 61:1779, 2015*

**Is It Time to Advance Pediatric NAFLD Diagnosis to the Magnetic Resonance Imaging Era?**

See Article on Page 1887

In 1910, an article appeared in the *Journal of Experimental Me*... entitled "T... The authors e... and appearance... found in 32... which conditi... attended by a... even in 1910, fatty liver was common and understood as pathologic. Today, the prevalence estimates of nonal...

Despite these early concerns regarding microscopic assessment, today's gold standard for the diagnosis of NAFLD remains histopathologic assessment of liver tissue in conjunction with clinical history.[5] However, it ...ws. Sampling ...of liver tissue ...atosis location ... interobserver ...s) have been ...ictured valida... ...ts.[6] While a κ of 0.79 is notable, it remains a subjective gold standard with limited utility as a comparator.

**"...superiority of MR-based methods (both MRI, MRS) over ultrasound is clear"**

HEPATOLOGY

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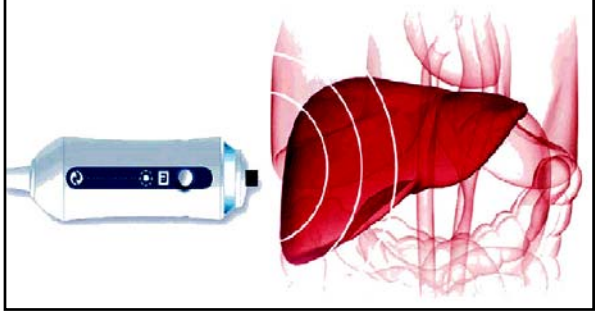
**"...superiority of MR-based methods (both MRI, MRS) over ultrasound is clear"**

**...won't replace Liver Biopsy**

## Assess Liver Stiffness; Correlates with fibrosis



CLINICAL AND LABORATORY OBSERVATIONS www.jpeds.com • THE JOURNAL OF PEDIATRICS

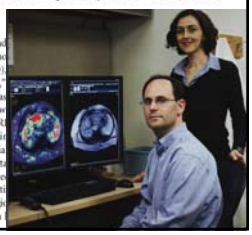
*Xanthakos, J Peds 164:186, 2014*

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

Stavra A. Xanthakos, MD, MS[1], Daniel J. Podberesky, MD[2], Suraj D. Serai, PhD[2], Lili Miles, MD[3], Eileen C. King, PhD[4], William F. Balistreri, MD[1], and Rohit Kohli, MBBS, MS[1]

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. (*J Pediatr 2014;164:186-8*).

The management of chronic liver diseases in children is impeded by lack of validated noninvasive biomarkers of histologic severity, necessitating invasive and costly liver biopsies. An accurate noninvasive method to detect significant liver fibrosis would reduce dependence on liver biopsies, facilitate the conduct of pediatric randomized clinical trials, and improve the ability to track clinical outcomes. Magnetic resonance elastography (MRE) has been shown to accurately detect significant hepatic fibrosis in adults,[1,2] but the feasibility of MRE and thresholds for detecting hepatic fibrosis in children are unknown. The aim of this pilot study was to evaluate the accuracy of MRE in detecting hepatic fibrosis in children. We hypothesized that MRE would have good accuracy (area under the receiver operating char-



HEPATOLOGY

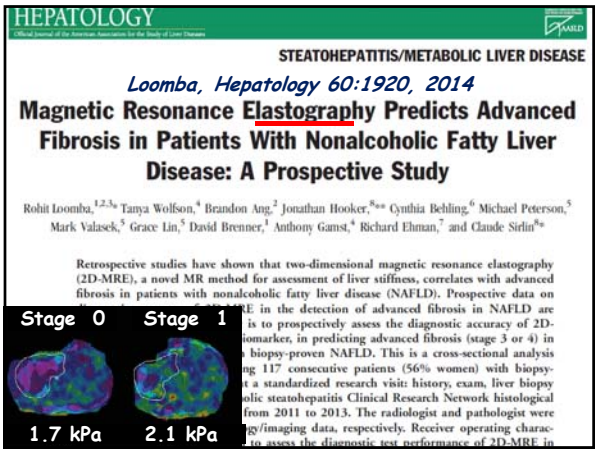
STEATOHEPATITIS/METABOLIC LIVER DISEASE

*Loomba, Hepatology 60:1920, 2014*

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

Rohit Loomba,[1,2,3]* Tanya Wolfson,[4] Brandon Ang,[2] Jonathan Hooker,[8]** Cynthia Behling,[6] Michael Peterson,[5] Mark Valasek,[5] Grace Lin,[5] David Brenner,[1] Anthony Gamst,[4] Richard Ehman,[7] and Claude Sirlin[8]*

**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 needed. The aim of this study is to prospectively assess the diagnostic accuracy of 2D-MRE, a noninvasive imaging biomarker, in predicting advanced fibrosis (stage 3 or 4) in well-characterized patients with biopsy-proven NAFLD. This is a cross-sectional analysis of a prospective study including 117 consecutive patients (56% women) with biopsy-proven NAFLD who underwent a standardized research visit: history, exam, liver biopsy assessment (using the nonalcoholic steatohepatitis Clinical Research Network histological scoring system), and 2D-MRE from 2011 to 2013. The radiologist and pathologist were blinded to clinical and pathology/imaging data, respectively. Receiver operating characteristics (ROCs) were examined to assess the diagnostic test performance of 2D-MRE in**


HEPATOLOGY
STEATOHEPATITIS/METABOLIC LIVER DISEASE
Loomba, Hepatology 60:1920, 2014
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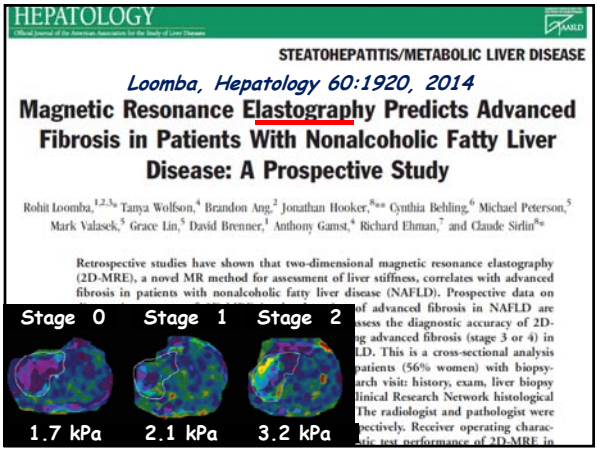
Stage 0
Stage 1
1.7 kPa
2.1 kPa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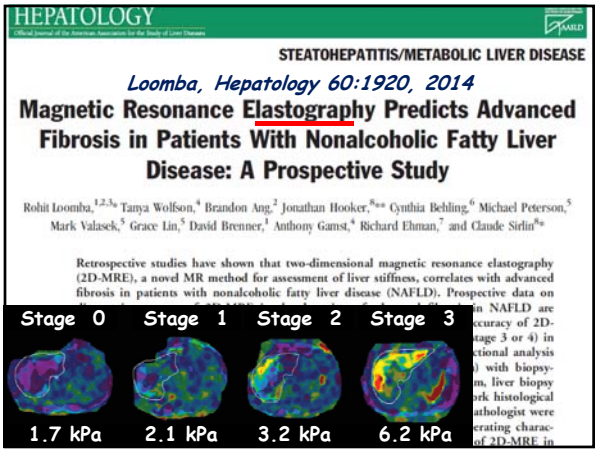
Stage 0
Stage 1
Stage 2
1.7 kPa
2.1 kPa
3.2 kPa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Stage 1
Stage 2
Stage 3
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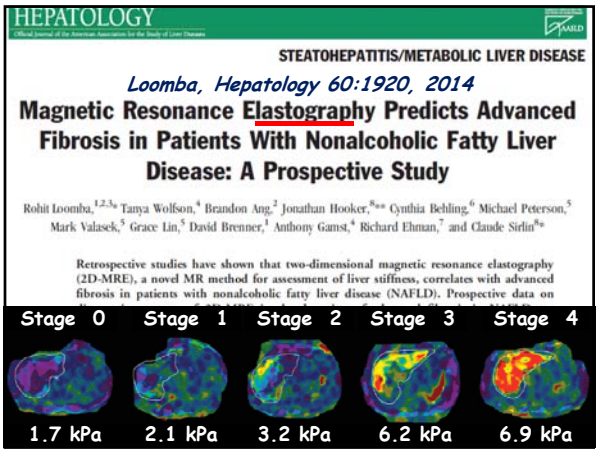
2.1 kPa
3.2 kPa
6.2 kPa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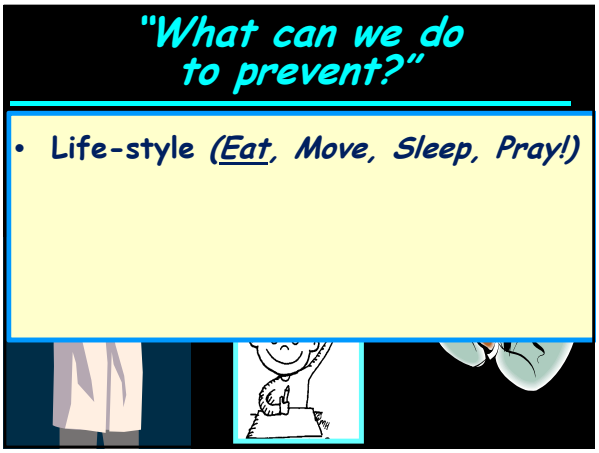
Stage 0
Stage 1
Stage 2
Stage 3
Stage 4
1.7 kPa
2.1 kPa
3.2 kPa
6.2 kPa
6.9 kPa


"What can we do to prevent?"


"What can we do to prevent?"
• Life-style (Eat, Move, Sleep, Pray!)

## "What can we do to prevent?"

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

TIME Health

## Liver Disease Is Yet Another Reason to Sit Less

September 15, 2015

**The list of conditions linked to sitting too much continues to grow, as scientists add another to t**

**Our Chairs Are Killing Us**
**>5hrs/day = ↑ risk of NAFLD**

In a study published in the *Journal of Hepatology*, researchers at led by Seungho Ryu at Kangbuk Samsung Hospital and Sungkyunkwan University report that too many hours spent sitting can increase the risk of developing non-alcoholic fatty liver disease (NAFLD). NAFLD is a condition in which excess fat builds up in the liver; in some cases the accumulation can cause scarring

ARTICLE IN PRESS

Research Article

EASL JOURNAL OF HEPATOLOGY

## Relationship of sitting time and physical activity with non-alcoholic fatty liver disease

Seungho Ryu[1,2,3,*], Yoosoo Chang[1,2,3,*], Hyun-Suk Jung[2], Kyung Eun Yun[2], Min-Jung Kwon[2,4], Yuni Choi[2], Chan-Won Kim[2], Juhee Cho[2,3], Byung-Seong Suh[2], Yong Kyun Cho[5], Eun Chul Chung[2,6], Hocheol Shin[2,7], Yeon Soo Kim[8]

[1]Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, South Korea; [2]Center for Cohort Studies, Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, South Korea; [3]Department of Clinical Research Design & Evaluation, SAIHST, Sungkyunkwan University, Seoul, South Korea; [4]Department of Laboratory Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, South Korea; [5]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, South Korea; [6]Department of Radiology, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, South Korea; [7]Department of Family Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, South Korea; [8]Department of Physical Education, Seoul National University, Seoul, South Korea

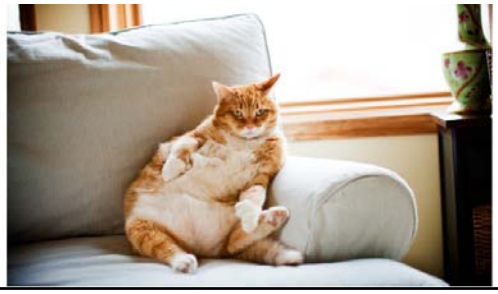
**…positive relationship**

*Ryu, Journal of Hepatology (in press October 2015)*

Well — The New York Times

## Sit Less, Live Longer?

By GRETCHEN REYNOLDS September 17, 2015



Well — The New York Times

PHYS ED

September 23, 2015

## Sitting Is Bad for Children, Too

By GRETCHEN REYNOLDS SEPTEMBER 23, 2015 5:45 AM

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

*Katzmarzyk, Med Sci Sports Exerc, 47:2062, 2015*

**Exploring the Adolescent Fall in Physical Activity: A 10-yr Cohort Study (EarlyBird 41)**

*KMetcalf, Med Sci Sports Exerc, 47:2084, 2015*

**Impact of prolonged sitting on vascular function in young girls.**

Ali M McManus[1], Philip N Ainslie[1], Daniel J Green[2,3], Ryan G Simair[1], Kurt Smith[1]

*McManus, Experimental Physiology (in press – October 2015)*

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

*Katzmarzyk, Med Sci Sports Exerc, 47:2062, 2015*

**Exploring the Adole**
**Activity: A**

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

**Imp** …cular function in young girls.

Ali M …, Philip N Ainslie[1], Daniel J Green[2,3], Ryan G Simair[1], Kurt Smith[1]

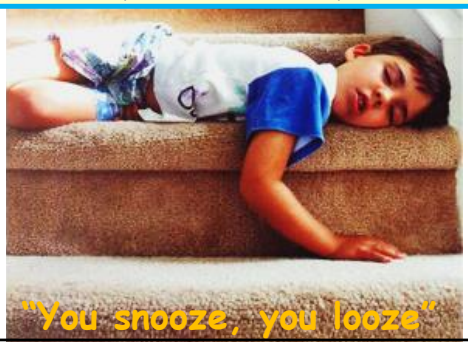
*McManus, Experimental Physiology (in press – October 2015)*

## *"What can we do to prevent?"*

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

**Short sleep duration in early childhood independently associated with obesity**

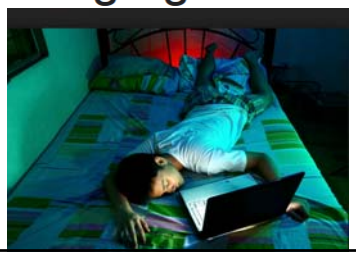
*Bonuck, J. Pediatr. 166:632, 2014*



CBSNEWS Video | US | World | Politics

By ASHLEY WELCH / CBS NEWS / October 2, 2015, 6:14 PM

# Late bedtimes for teens could lead to weight gain over time



CBSNEWS Video | US | World | Politics

By ASHLEY WELCH / CBS NEWS / October 2, 2015, 6:14 PM

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

Lauren D. Asarnow, MA[1], Eleanor McGlinchey, PhD[2], Allison G. Harvey, PhD[1]

[1]Department of Psychology, University of California, Berkeley, CA; [2]Department of Psychiatry, Division of Child and Adolescent Psychiatry, Columbia University, New York State Psychiatric Institute, New York, NY

**Objectives:** The aim of the current study was to examine the longitudinal relationship between bedtimes and body mass index (BMI) from adolescence to adulthood in a nationally representative sample.

**Design:** Three waves of data from the National Longitudinal Study of Adolescent Health were used to assess the bedtimes and BMI of 3,342 adolescents between 1994 and 2009. Hypotheses were tested with hierarchical linear models using a two-level, random intercept and slopes model.

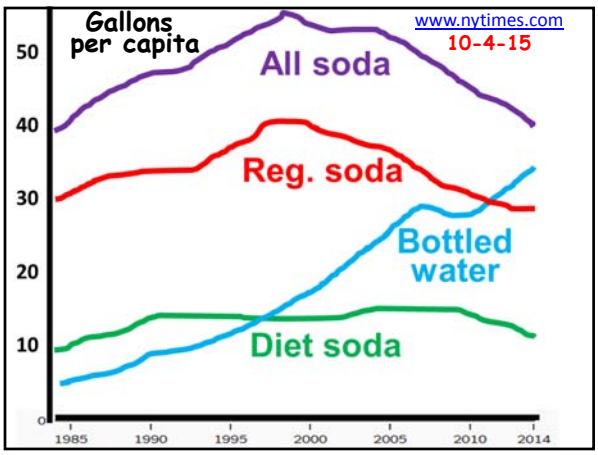
**Results:** Later ave... in BMI over time (b = 0.035 kg/m² p... results remained significant after co... exercise frequency did not attenuate t... significant partial mediator of the rel...

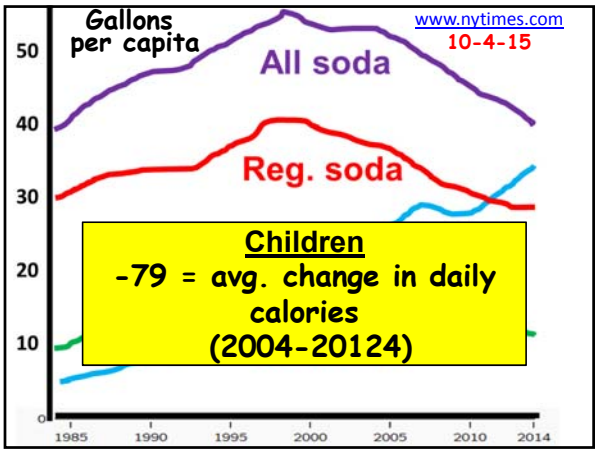
**Conclusions:** The results highlight bedtimes as a potential target for weight management during adolescence and during the transition to adulthood.

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
  - *Ma, Journal of Hepatology 63:462, 2015*




## "What can we do to prevent?"

- Life-style *(Eat, Move, Sleep, Pray!)*
- Avoid sugar-sweetened beverages
  - *Ma, Journal of Hepatology 63:462, 2015*
- "Avoid" antibiotics
  - *Cox, Cell 158:705, 2014*
  - *Bailey, JAMA Pediatrics, 168:1063, 2014*

## "What can we do to treat?"

- Probiotics / Prebiotics
- Fatty Acids (Omega-3, DHA)
- Antioxidants (Vitamin E)
- Antifibrotics
- BARIATRIC approaches
- ? Pharmacologic

EDITORIAL

## Another Agent for Obesity — Will This Time Be Different?

Elias 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 incessant enticements to sit and an unprecedented availability, at low or no cost, of foods and beverages rich in poorly satiating calories. These rapid environmental changes interact with preexisting genetic tendencies, yet in a time- obesity remain 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,[6] but the potential side effects are of concern. Furthermore, performing bariatric surgery in approximately 400 million obese persons worldwide is not feasible.

Enter another approach: glucagon-like pep-

*Siraj, NEJM 373:82, 2015*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2015 VOL. 373 NO. 1

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

Xavier Pi-Sunyer, M.D., Arne Astrup, M.D., D.M.Sc., Ken Fujioka, M.D., Frank Greenway, M.D., Alfredo Halpern, M.D., Michel Krempf, M.D., Ph.D., David C.W. Lau, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D., Rafael Violante Ortiz, M.D., Christine Bjørn Jensen, M.D., Ph.D., and John P.H. Wilding, D.M., for the SCALE Obesity and Prediabetes NN8022-1839 Study Group*

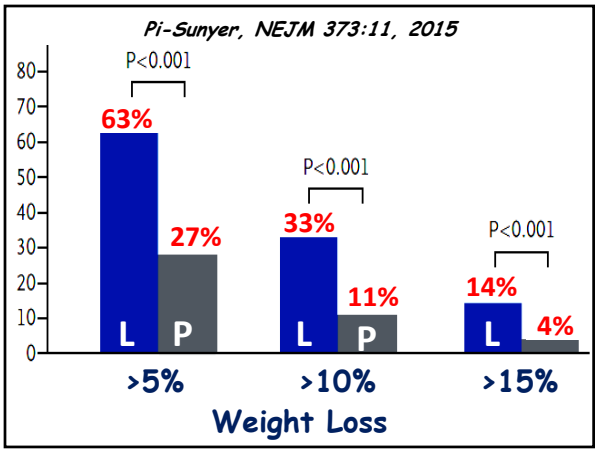
*Pi-Sunyer, NEJM 373:11, 2015*

BACKGROUND

Obesity is a chronic disease with serious health consequences, but weight loss is difficult to maintain through lifestyle intervention alone. Liraglutide, a glucagon-

- Glucagon-like peptide-1 analogue
- "mimics effects of satiety hormone"

*Pi-Sunyer, NEJM 373:11, 2015*



NAFLD

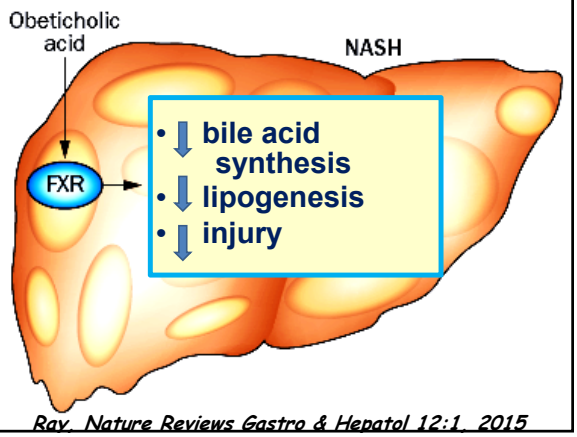
## Obeticholic acid for the treatment of fatty liver disease—NASH no more?

***Ray, Nature Reviews Gastro & Hepatol 12:1, 2015***

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.

NAFLD, which encompasses a spectrum of disease from simple steatosis to NASH, fibrosis and cirrhosis, is becoming increasingly common worldwide. With no approved agents for NAFLD 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 to

In the primary intention-to-treat analysis, 50 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 the proportion of patients with complete resolution of NASH did not differ between those receiving placebo and




***Ray, Nature Reviews Gastro & Hepatol 12:1, 2015***

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

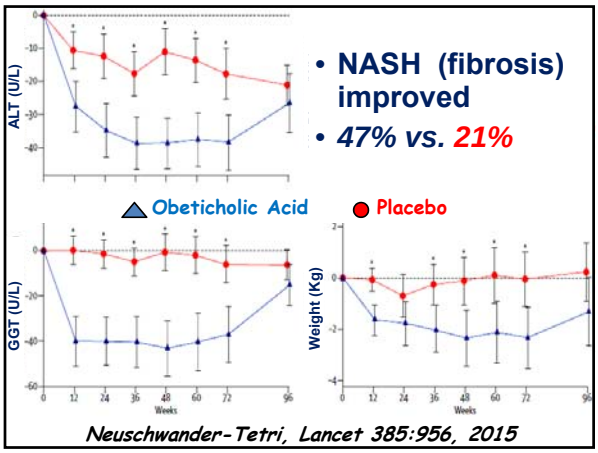
*Brent A Neuschwander-Tetri, Rohit Loomba, Arun J Sanyal, Joel E Lavine, Mark L Van Natta, Manal F Abdelmalek, Naga Chalasani, Srinivasan Dasarathy, Anna Mae Diehl, Bilal Hameed, Kris V Kowdley, Arthur McCullough, Norah Terrault, Jeanne M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network**

***Neuschwander-Tetri, Lancet 385:956, 2015***

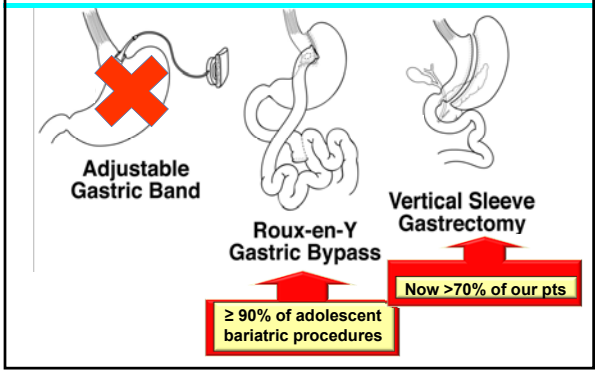
**Summary**

**Background** The bile acid derivative 6-ethylchenodeoxycholic acid (obeticholic acid) is a potent activator of the farnesoid X nuclear receptor that reduces liver fat and fibrosis in animal models of fatty liver disease. We assessed the efficacy of obeticholic acid in adult patients with non-alcoholic steatohepatitis.

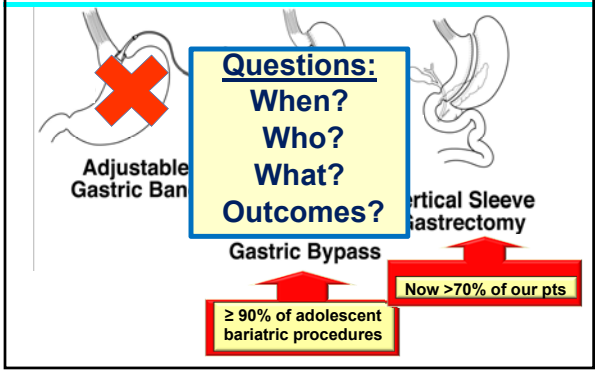
**Methods** We did a multicentre, double-blind, placebo-controlled, parallel group, randomised clinical trial at medical centres in the USA in patients with non-cirrhotic, non-alcoholic steatohepatitis to assess treatment with obeticholic acid given orally (25 mg daily) or placebo for 72 weeks. Patients were randomly assigned 1:1 using a computer-generated, centrally administered procedure, stratified by clinical centre and diabetes status. The primary outcome measure was improvement in centrally scored liver histology defined as a decrease in non-alcoholic fatty liver disease activity score by at least 2 points without worsening of fibrosis from baseline to the end of treatment. A planned interim analysis of change in alanine aminotransferase at 24 weeks undertaken before end-of-treatment (72 weeks) biopsies supported the decision to continue the trial (relative change in alanine aminotransferase −24%, 95% CI −45 to −3). A planned interim analysis of the primary outcome showed improved efficacy of obeticholic acid (p=0·0024) and supported a decision not to do end-of-treatment biopsies and end treatment early in 64 patients, but to continue the trial to obtain the 24-week post-treatment measures. Analyses were done by intention-to-treat. This trial was registered with ClinicalTrials.gov, number NCT01265498.

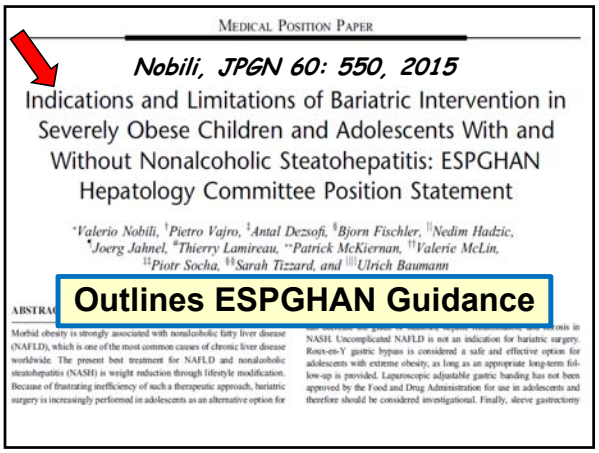



## Adolescent Bariatric Procedures




## Adolescent Bariatric Procedures





MEDICAL POSITION PAPER

*Nobili, JPGN 60: 550, 2015*

Indications and Limitations of Bariatric Intervention in Severely Obese Children and Adolescents With and Without Nonalcoholic Steatohepatitis: ESPGHAN Hepatology Committee Position Statement

*Valerio Nobili, Pietro Vajro, Antal Dezsofi, Bjorn Fischler, Nedim Hadzic, Joerg Jahnel, Thierry Lamireau, Patrick McKiernan, Valerie McLin, Piotr Socha, Sarah Tizzard, and Ulrich Baumann*

**Outlines ESPGHAN Guidance**

ABSTRAC

Morbid obesity is strongly associated with nonalcoholic fatty liver disease (NAFLD), which is one of the most common causes of chronic liver disease worldwide. The present best treatment for NAFLD and nonalcoholic steatohepatitis (NASH) is weight reduction through lifestyle modification. Because of frustrating inefficiency of such a therapeutic approach, bariatric surgery is increasingly performed in adolescents as an alternative option for

NASH. Uncomplicated NAFLD is not an indication for bariatric surgery. Roux-en-Y gastric bypass is considered a safe and effective option for adolescents with extreme obesity, as long as an appropriate long-term follow-up is provided. Laparoscopic adjustable gastric banding has not been approved by the Food and Drug Administration for use in adolescents and therefore should be considered investigational. Finally, sleeve gastrectomy

NASPGHAN 2015

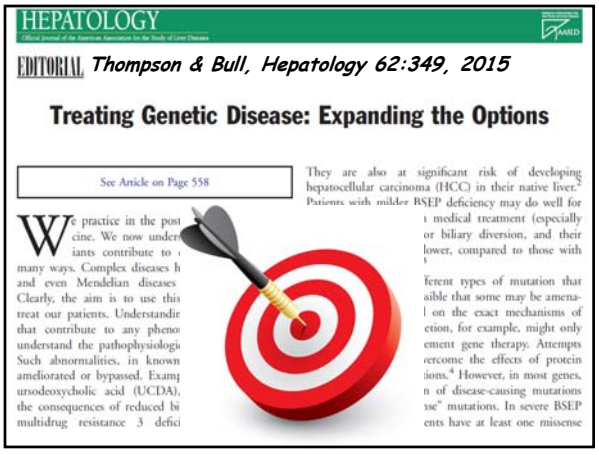
*Annual Meeting & Postgraduate Course*

**"NASPYS"**

**Strategy of the Year**

**Targeting MLD**

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



HEPATOLOGY

Official Journal of the American Association for the Study of Liver Diseases

EDITORIAL *Thompson & Bull, Hepatology 62:349, 2015*

**Treating Genetic Disease: Expanding the Options**

See Article on Page 558

W e practice in the post cine. We now under iants contribute to many ways. Complex diseases h and even Mendelian diseases Clearly, the aim is to use this treat our patients. Understandir that contribute to any phenot understand the pathophysiologi Such abnormalities, in known ameliorated or bypassed. Exam ursodeoxycholic acid (UCDA), the consequences of reduced bi multidrug resistance 3 defici

They are also at significant risk of developing hepatocellular carcinoma (HCC) in their native liver.[2] Patients with milder BSEP deficiency may do well for medical treatment (especially or biliary diversion, and their lower, compared to those with ferent types of mutation that aible that some may be amena- on the exact mechanisms of etion, for example, might only ement gene therapy. Attempts ercome the effects of protein ions.[4] However, in most genes, n of disease-causing mutations se" mutations. In severe BSEP ents have at least one missense

HEPATOLOGY

*Gonzales, Hepatology 62:558, 2015*

**Targeted Pharmacotherapy in Progressive Familial Intrahepatic Cholestasis Type 2: Evidence for Improvement of Cholestasis With 4-Phenylbutyrate**

Emmanuel Gonzales,[1,2] Brigitte Grosse,[2] Brice Schuller,[2] Anne Davit-Spraul,[3] Filomena Conti,[4]

HEPATOLOGY

*Varma, Hepatology 62:198, 2015*

**Retargeting of Bile Salt Export Pump and Favorable Outcome in Children With Progressive Familial Intrahepatic Cholestasis Type 2**

Sharat Varma,[1] Nicole Revencu,[2] Xavier Stephenne,[1] Isabelle Scheers,[1] Françoise Smets,[1] Ana Beleza-Meireles,[2] Raymond Reding,[3] Tania Roskams,[4] and Etienne M. Sokal[1]

HEPATOLOGY

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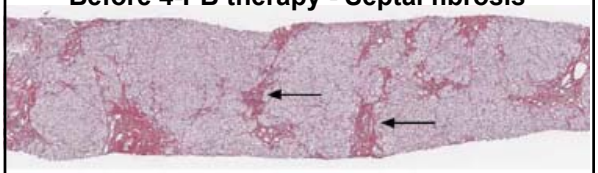
- **4-PB retargets mutated BSEP in pts with PFIC2**
- **Bile secretion & PRURITUS improve**

**Retargeting of Bile Salt Export Pump and Favorable Outcome in Children With Progressive Familial Intrahepatic Cholestasis Type 2**

Sharat Varma,[1] Nicole Revencu,[2] Xavier Stephenne,[1] Isabelle Scheers,[1] Françoise Smets,[1] Ana Beleza-Meireles,[2] Raymond Reding,[3] Tania Roskams,[4] and Etienne M. Sokal[1]

**Before 4-PB therapy - Septal fibrosis**



**3 mos after 4-PB therapy**

*Gonzales, Hepatology 62:558, 2015*

nature publishing group

**Review**

*Wang & Perlmutter, Pediatric Research 75:133, 2014*

## Targeting intracellular degradation pathways for treatment of liver disease caused by α1-antitrypsin deficiency

**Carbamazepine**

Yan Wang[1,2] and David H. Perlmutter[1–3]

The classic form of α1-antitrypsin deficiency (ATD) is a well-known genetic cause of severe liver disease in childhood. A point mutation alters the folding of a hepatic secretory glycoprotein such that the protein is prone to misfolding and polymerization. Liver injury, characterized predominantly by fibrosis/cirrhosis and carcinogenesis, is caused by the p… of polymerized mutant α1-antitrypsin Z (ATZ), … lates in the endoplasmic reticulum (ER) of hepa… intracellular pathways have been shown to be… disposal of ATZ after it accumulates in the ER, … appears to be specialized for disposal of insolubl… Recently, we have found that drugs that enhanc… the autophagic pathway reduce the cellular loa… and reverse hepatic fibrosis in a mouse model …

several forms of ATD, including a classic form in which a point mutation leads to altered folding during biogenesis. In this classic form, the mutant protein, α1-antitrypsin Z (ATZ), accumulates in the early compartments of the secretory pathway, especially the endoplasmic reticulum (ER), while the amount of AT …edly reduced. Serum levels of AT in affected … in the range of 10–15% of those in normal … did not take long to realize that susceptibility …OPD is due to the proteolytic effect of unin… …il proteases on the connective tissue matrix of … …ilization led to the protease–antiprotease para… …mesis of COPD and to the rationale for use of … …rapy with purified α1-antitrypsin for patients … to ATD (reviewed in ref. 4).

EDITORIALS

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

**LAL-D**

Daniel J. Rader, M.D.

*Rader, N Engl J Med 373:1071, 2015*

There are more than 50 different lysosomal storage diseases, genetic disorders characterized by lysosomal accumulation of substrate.[1] Phenotypes vary widely, depending on the specific cell types affected. Enzyme-replacement therapy has been transformational in the treatment of … somal storage diseases[2]; however, enz… ment therapy is currently approved a… cially available for only 7 lysoso… diseases.

The principle of enzyme-replacem… is that after administration of a reco… zyme, it is taken up by target cells a…

Options for the clinical treatment of patients with lysosomal acid lipase deficiency are currently limited. Statins do not slow progression of the liver disease and actually could hasten progression by increasing LDL cholesterol recep… uptake of lipoproteins[3] (a similar …ld be made regarding inhibitors … convertase subtilisin–kexin type 9 … cholesterol-absorption inhibitor … some efficacy on liver lipid and …transferase levels in a mouse model …se,[3] but clinical experience with …patients with lysosomal acid lipase

*Reiner, Atherosclerosis 235:21, 2014*

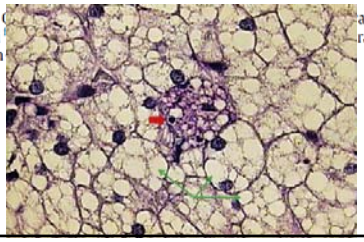
Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

## Lysosomal acid lipase deficiency – An under-recognized cause of dyslipidaemia and liver dysfunction

Željko Reiner[a,*], … an[d], Kees Hovi…
Stefano Bertolini[… ra[h], John Hami…
Terence Eagleton…



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

**Authors:**

Barbara K. **Burton**, MD[1]; Patrick B. **Deegan**, MD[2]; Gregory M. **Enns**, MD[3]; Ornella **Guardamagna**, MD[4]; Simon **Horslen**, MB, ChB, FRCPCH[5]; Gerard K. **Hovingh**, MD[6]; Steve J. **Lobritto**, MD[7]; Vera **Malinova**, MD[8]; Valerie A. **McLin**, MD[9]; Julian **Raiman**, MD[10]; Maja **Di Rocco**, MD[11]; Saikat **Santra**, MD[12]; Reena **Sharma**, MBBS[13]; Jolanta **Sykut-Cegielska**, MD[14]; Chester B. **Whitley**, MD[15]; Stephen **Eckert**, PhD[16]; Vassili **Valayannopoulos**, MD[17]; Anthony G. **Quinn**, MBChB PhD FRCP[16]

*Burton, JPGN, in press Oct 2015*

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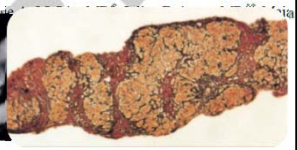

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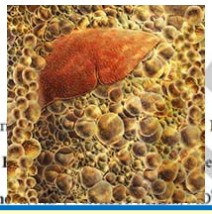


**Authors:**

Barbara K. **Burton**, MD[1]; Patr

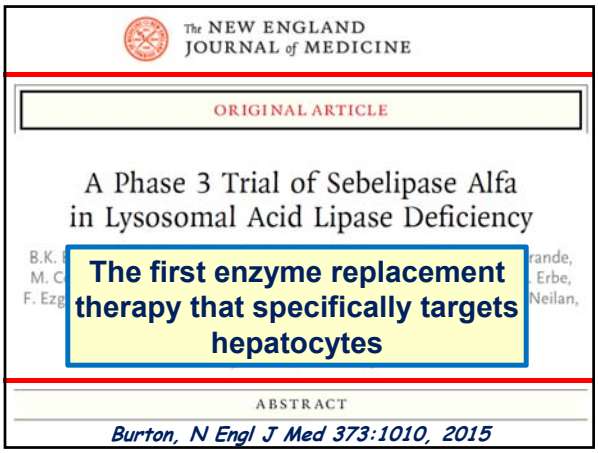
Enns, MD[3]; Ornella **Guardamagna**, MD[4]; Simon

erard K. **Hovingh**, MD[6]; Steve J. **Lobritto**, MD[7]; Vera **Malin**

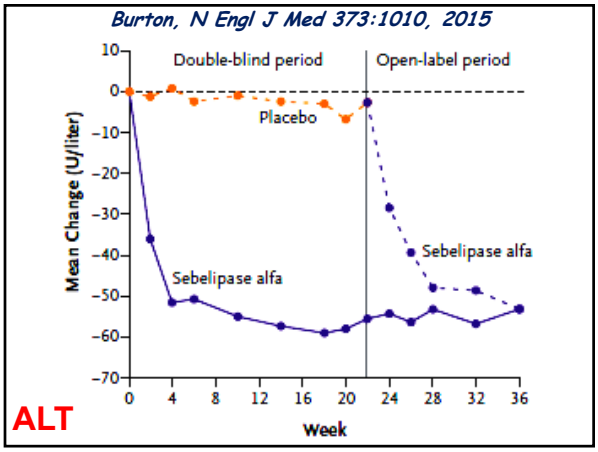
D[9]; Julian **Raiman**, MD[10]; Maja

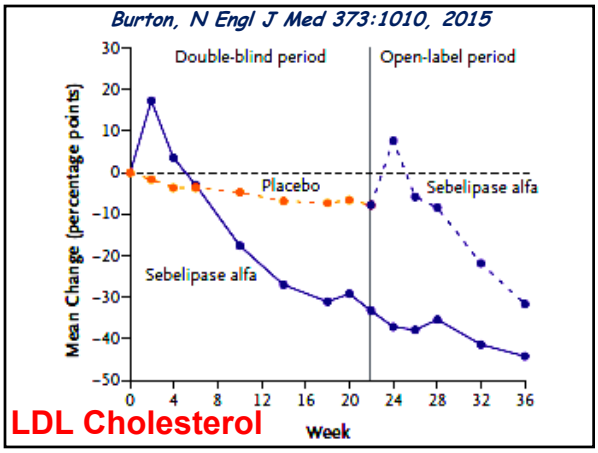
- **Serum ALT elevated in 92%**
- **Elevated LDL (64%); low HDL (44%)**
- **Steatosis (87%) and/or fibrosis (52%)**

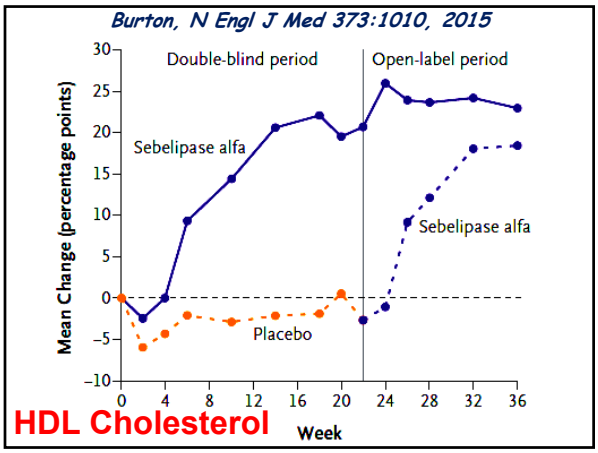
*Burton, JPGN, in press Oct 2015*

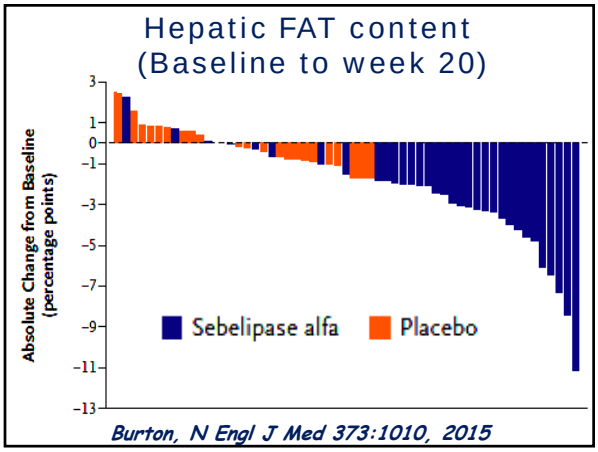



*Burton, N Engl J Med 373:1010, 2015*

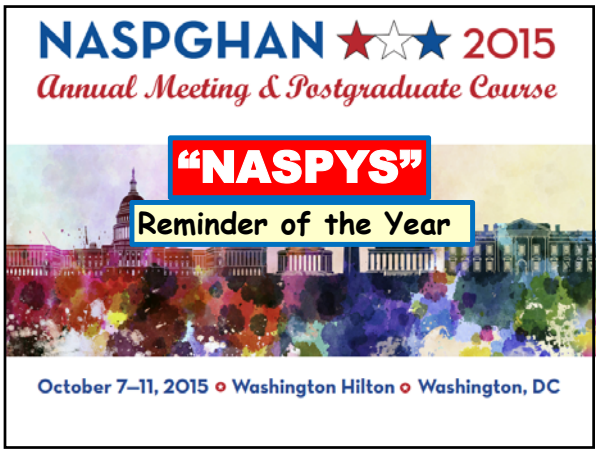


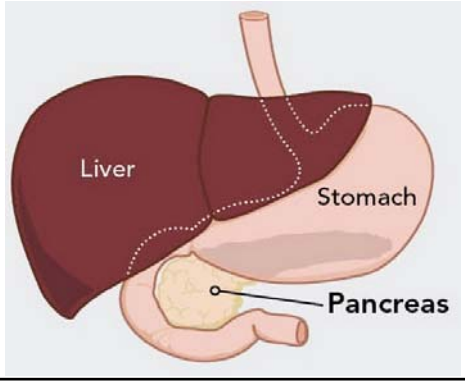

Burton, N Engl J Med 373:1010, 2015
Double-blind period
Open-label period
Sebelipase alfa
Sebelipase alfa
Placebo
Mean Change (percentage points)
Week
HDL Cholesterol


Hepatic FAT content
(Baseline to week 20)
Absolute Change from Baseline (percentage points)
Sebelipase alfa
Placebo
Burton, N Engl J Med 373:1010, 2015


"Save Livers
Save Lives"




## Don't Forget the Pancreas!

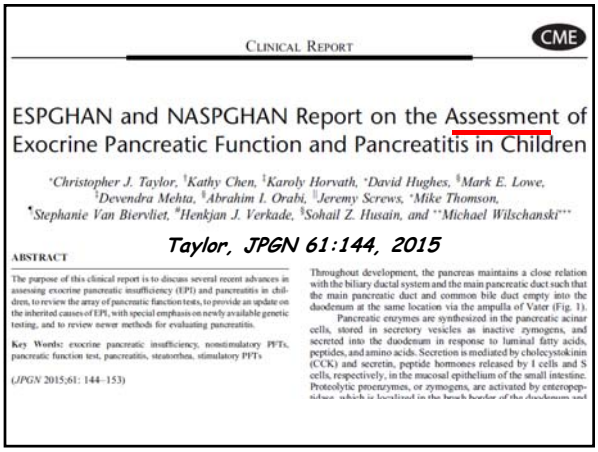



## Progress, Opportunities, Challenges, Collaborations

- NASPGHAN Pancreas Committee

## Progress, Opportunities, Challenges, Collaborations

- NASPGHAN Pancreas Committee
- **Guidelines**



CLINICAL REPORT

CME

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

*Christopher J. Taylor, †Kathy Chen, †Karoly Horvath, *David Hughes, §Mark E. Lowe, ‖Devendra Mehta, ¶Abrahim I. Orabi, ‖Jeremy Screws, *Mike Thomson, ¶Stephanie Van Biervliet, #Henkjan J. Verkade, §Sohail Z. Husain, and **Michael Wilschanski***

*Taylor, JPGN 61:144, 2015*

ABSTRACT

The purpose of this clinical report is to discuss several recent advances in assessing exocrine pancreatic insufficiency (EPI) and pancreatitis in children, to review the array of pancreatic function tests, to provide an update on the inherited causes of EPI, with special emphasis on newly available genetic testing, and to review newer methods for evaluating pancreatitis.

Key Words: exocrine pancreatic insufficiency, nonstimulatory PFTs, pancreatic function test, pancreatitis, steatorrhea, stimulatory PFTs

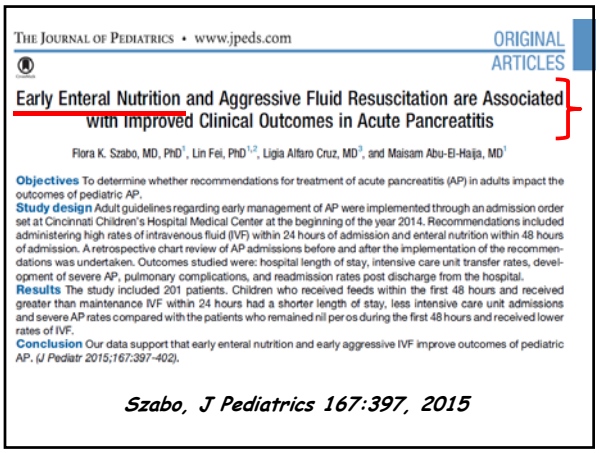
(*JPGN* 2015;61: 144–153)

Throughout development, the pancreas maintains a close relation with the biliary ductal system and the main pancreatic duct such that the main pancreatic duct and common bile duct empty into the duodenum at the same location via the ampulla of Vater (Fig. 1).

Pancreatic enzymes are synthesized in the pancreatic acinar cells, stored in secretory vesicles as inactive zymogens, and secreted into the duodenum in response to luminal fatty acids, peptides, and amino acids. Secretion is mediated by cholecystokinin (CCK) and secretin, peptide hormones released by I cells and S cells, respectively, in the mucosal epithelium of the small intestine. Proteolytic proenzymes, or zymogens, are activated by enteropep-

## Progress, Opportunities, Challenges, Collaborations

- NASPGHAN Pancreas Committee
- Guidelines
- **Studies**



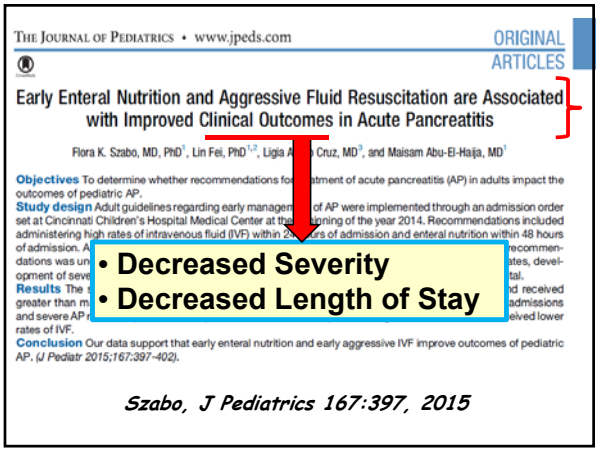
THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

**Early Enteral Nutrition and Aggressive Fluid Resuscitation are Associated with Improved Clinical Outcomes in Acute Pancreatitis**

Flora K. Szabo, MD, PhD[1], Lin Fei, PhD[1,2], Ligia Alfaro Cruz, MD[3], and Maisam Abu-El-Haija, MD[1]

**Objectives** To determine whether recommendations for treatment of acute pancreatitis (AP) in adults impact the outcomes of pediatric AP.
**Study design** Adult guidelines regarding early management of AP were implemented through an admission order set at Cincinnati Children's Hospital Medical Center at the beginning of the year 2014. Recommendations included administering high rates of intravenous fluid (IVF) within 24 hours of admission and enteral nutrition within 48 hours of admission. A retrospective chart review of AP admissions before and after the implementation of the recommendations was undertaken. Outcomes studied were: hospital length of stay, intensive care unit transfer rates, development of severe AP, pulmonary complications, and readmission rates post discharge from the hospital.
**Results** The study included 201 patients. Children who received feeds within the first 48 hours and received greater than maintenance IVF within 24 hours had a shorter length of stay, less intensive care unit admissions and severe AP rates compared with the patients who remained nil per os during the first 48 hours and received lower rates of IVF.
**Conclusion** Our data support that early enteral nutrition and early aggressive IVF improve outcomes of pediatric AP. (*J Pediatr 2015;167:397-402*).

***Szabo, J Pediatrics 167:397, 2015***



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

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- **Decreased Severity**
- **Decreased Length of Stay**

***Szabo, J Pediatrics 167:397, 2015***

## Progress, Opportunities, Challenges, Collaborations

- NASPGHAN Pancreas Committee
- Guidelines
- Studies
- **INSPPIRE (Pancreas)**

- **The International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium:**

ORIGINAL ARTICLE: GASTROENTEROLOGY

*Morinville, JPGN 59: 360, 2014*

## Design and Implementation of INSPPIRE

*Veronique D. Morinville, Mark E. Lowe, Monika Ahuja, Bradley Barth, Melena D. Bellin, Heather Davis, Peter R. Durie, Brian Finley, Douglas S. Fishman, Steven D. Freedman, Cheryl E. Gariepy, Matthew J. Giefer, Tanja Gonska, Melvin B. Heyman, Ryan Himes, Sohail Husain, Soma Kumar, Chee Y. Ooi, John F. Pohl, Sarah Jane Schwarzenberg, David Troendle, Steven L. Werlin, Michael Wilschanski, Elizabeth Yen, and Aliye Uc*

ABSTRACT

**Objectives:** Acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are rare and poorly understood diseases in children. Better under-

changes made into the REDCap database. Between September 1, 2012 and August 31, 2013, a total of 194 children were enrolled into the study

history, medications, hospitalizations, risk factors, diagnostic evaluation, treatments, and outcome information. Information collected in paper questionnaires was then transferred into Research Electronic Data Capture (REDCap), tabulated, and analyzed.

**Goal = develop Rx for recurrent acute and chronic pancreatitis in children**

Key Words: acute recurrent pancreatitis, children, chronic pancreatitis, database, questionnaire, registry

(*JPGN* 2014;59: 360–364)

ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

## Pediatric Chronic Pancreatitis Is Associated with Genetic Risk Factors and Substantial Disease Burden

Sarah Jane Schwarzenberg, MD[1,*], Melena Bellin, MD[1,*], Sohail Z. Husain, MD[2,*], Monika Ahuja, MCA[3], Bradley Barth, MD[4], Heather Davis, MD[5], Peter R. Durie, MD[5], Douglas S. Fishman, MD[6], Steven D. Freedman, MD[7], Cheryl E. Gariepy, MD[8], Matthew J. Giefer, MD[9], Tanja Gonska, MD[5], Melvin B. Heyman, MD, MPH[10], Ryan Himes, MD[6], Soma Kumar, MD[9],

*Schwarzenberg, Journal of Pediatrics 166:890, 2015*

**Objective** To determine the clinical presentation, diagnostic variables, risk factors, and disease burden in children with chronic pancreatitis.

**Study design** We performed a cross-sectional study of data from the International Study Group of Pediatric

**Insight into clinical presentations, diagnostic variables, risk factors, and disease burden**

the emergency department ($P = .01$), and experience hospitalizations ($P = .03$) compared with children with episodic pain. Thirty-three children (43%) underwent therapeutic endoscopic retrograde pancreatography; one or more pancreatic surgeries were performed in 30 (39%).

**Conclusions** Chronic pancreatitis occurs at a young age with distinct clinical features. Genetic and obstructive risk factors are common, and disease burden is substantial. (*J Pediatr 2015;166:890-6*).

## Risk factors for pancreatitis

*Schwarzenberg, Journal of Pediatrics 166:890, 2015*

| | |
|---|---|
| • Genetic | 67% |
| – PRSS1 | 43% |
| – SPINK1 | 19% |
| – CFTR | 14% |
| – CTRC | 3% |
| • Autoimmune | 4% |
| • Obstructive | 33% |
| – Pancreas divisum | 20% |
| – Sphincter of Oddi dysfunction | 1% |
| – Gallstones | 4% |
| – Pancreatic duct malunion | 4% |
| • Toxic/metabolic | 11% |
| – Alcohol (determined by doctor) | 1% |
| – Passive smoking (exposure) | 4% |
| – Hyperlipidemia, Meds, Metabolic disease | 1% each |
| • None cited | 11% |

NASPGHAN 2015

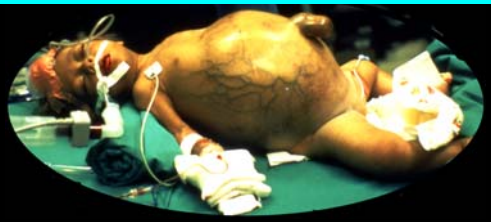
*Annual Meeting & Postgraduate Course*

**"NASPYS"**

**Opportunity for the Future**

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

*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 r… of the procedure. It is universally acknowled… before 60 days of age can improve the likelih… avoid liver transplant. The problem that we c… ce is late referral of patients with biliary atres… ning for this potentially devastating disease.

The lack of bile flow… ls—a reliable clue that obstruction is likely. I… n the first month after birth in patients with biliary atresia. Thus, the concept of using a stool color card for screenin… troduced to the local pop… 3 (*Screening* 1993;2:201-9… ng a prompt diagnosis an… based mass screening has subsequently been utilized in several other countries, also resulting in earlier referral of patients with biliary atresia.

**Early diagnosis of biliary atresia**

— William F. Balistreri, MD

*J Pediatr 166:784, 2015*

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

## Newborn Screen Can Detect Biliary Atresia

A simple and widely available screening test can identify biliary atresia in newborns with high sensitivity, researchers have found.

Biliary atresia (BA) is the leading indication for pediatric liver transplantation worldwide. The disease affects approximately one in 10,000 infants in the United States, and is characterized by rapid liver scarring. Although some countries use a stool color card to screen for BA, no such tool exists in the United States.

The sole accepted treatment for the… and emotional toll. We talk about it being rare, but it is 10 times more common than some of the diseases we currently do newborn screening for," said Ron Sokol, MD, section head of gastroenterology, hepatology and nutrition at Children's Hospital Colorado, in Aurora. "When an infant has elevated DB/CB levels in the first five days of life, it's something that needs to be followed up."

Stool color cards are being used in several countries and being tested in… others, and appear to be effective compared with no screening, Dr. Sokol said. "In Taiwan and Japan, the stool color card seems to get the children to Kasai surgery before 45 days on average, which is very good," he said.

Using DB or CB levels as a screening tool will require more study to assess its overall cost-effectiveness, he said. "This is an early study, but it's promising," Dr. Sokol said. "There's no reason we shouldn't be screening for BA, it's just…


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

*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

Yan-Hong Gu, MD, MSc, PhD[1,2], Koji Yokoyama, MD[3], Koichi Mizuta, MD, PhD[4], Takashi Tsuchioka, MD, PhD[5], Toyoichiro Kudo, MD, PhD[6], Hideyuki Sasaki, MD, PhD[7], Masaki Nio, MD, PhD[7], Julian Tang, PhD[8], Takayoshi Ohkubo, MD, PhD[1], and Akira Matsui, MD, DMSci[6]

**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 at Kasai procedure and the long-term probabilities of native liver survival were investigated.

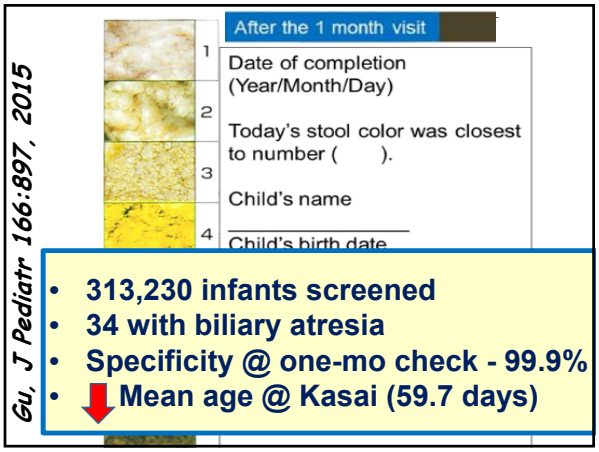
**Study design** From 1994 to 2011, the stool color card was distributed to all pregnant women in Tochigi Prefecture, Japan. Before or during the postnatal 1-month health checkup, the mothers returned the completed stool color card to the attending pediatrician or obstetrician. All suspected cases of biliary atresia were referred for further examination. Diagnosis was confirmed by laparotomy or operative cholangiography for high-risk cases before the Kasai procedure. Patients with biliary atresia were followed from the date of their Kasai procedure until liver transplantation, death, or October 31, 2013, whichever comes sooner.

**Results** A total of 313230 live born infants were screened; 34 patients with biliary atresia were diagnosed. The sensitivity and specificity of stool color card screening at the 1-month check-up was 76.5% (95% CI 62.2-90.7) and 99.9% (95% CI 99.9-100.0), respectively. Mean age at the time of Kasai procedure was 59.7 days. According to Kaplan-Meier analysis, the native liver survival probability at 5, 10, and 15 years was 87.6%, 76.9%, and 48.5%, respectively.

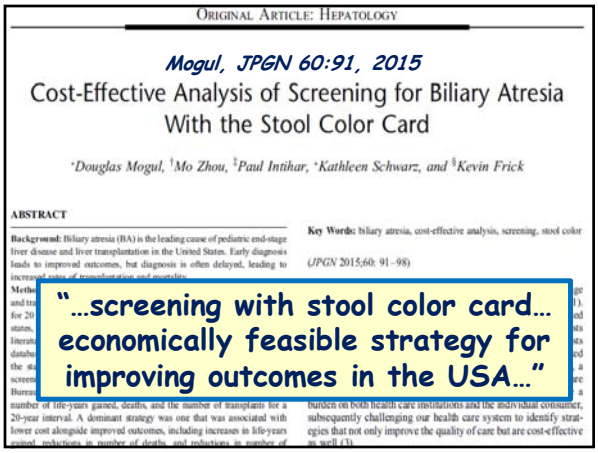
**Conclusions** The sensitivity and specificity of the stool color card have been demonstrated by our 19-year cohort study. We found that the timing of Kasai procedure and long-term native liver survival probabilities were improved, suggesting the beneficial effect of stool color card screening. (*J Pediatr 2015;166:897-902*).

*Gu, J Pediatr 166:897, 2015*


*Gu, J Pediatr 166:897, 2015*




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



ORIGINAL ARTICLE: HEPATOLOGY

*Mogul, JPGN 60:91, 2015*

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

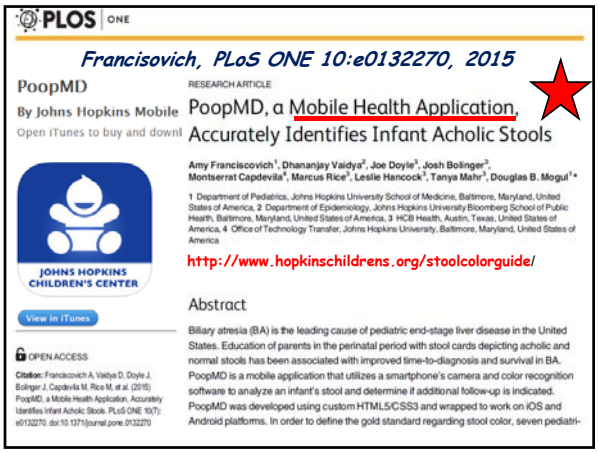
*Douglas Mogul, Mo Zhou, Paul Intihar, Kathleen Schwarz, and Kevin Frick*

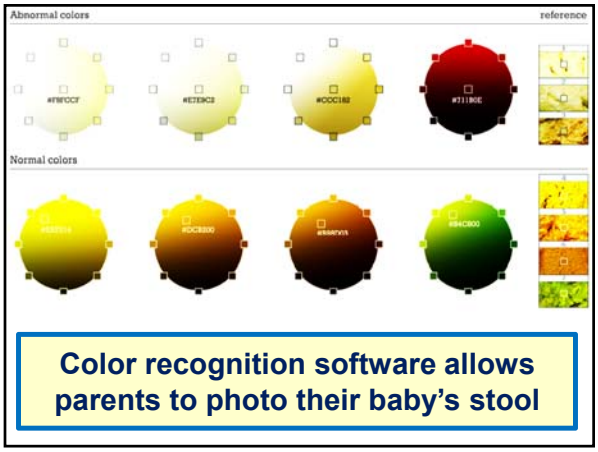
ABSTRACT

Key Words: biliary atresia, cost-effective analysis, screening, stool color

(*JPGN* 2015;60: 91–98)

**"…screening with stool color card… economically feasible strategy for improving outcomes in the USA…"**


PLOS ONE
Francisovich, PLoS ONE 10:e0132270, 2015
PoopMD
By Johns Hopkins Mobile
Open iTunes to buy and downl
RESEARCH ARTICLE
PoopMD, a Mobile Health Application, Accurately Identifies Infant Acholic Stools
Amy Franciscovich[1], Dhananjay Vaidya[2], Joe Doyle[3], Josh Bolinger[3], Montserrat Capdevila[4], Marcus Rice[4], Leslie Hancock[3], Tanya Mahr[3], Douglas B. Mogul[1]*
1 Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, 2 Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, United States of America, 3 HCB Health, Austin, Texas, United States of America, 4 Office of Technology Transfer, Johns Hopkins University, Baltimore, Maryland, United States of America
http://www.hopkinschildrens.org/stoolcolorguide/
JOHNS HOPKINS CHILDREN'S CENTER
View in iTunes
OPEN ACCESS
Citation: Franciscovich A, Vaidya D, Doyle J, Bolinger J, Capdevila M, Rice M, et al. (2015) PoopMD, a Mobile Health Application, Accurately Identifies Infant Acholic Stools. PLoS ONE 10(7): e0132270. doi:10.1371/journal.pone.0132270
Abstract
Biliary atresia (BA) is the leading cause of pediatric end-stage liver disease in the United States. Education of parents in the perinatal period with stool cards depicting acholic and normal stools has been associated with improved time-to-diagnosis and survival in BA. PoopMD is a mobile application that utilizes a smartphone's camera and color recognition software to analyze an infant's stool and determine if additional follow-up is indicated. PoopMD was developed using custom HTML5/CSS3 and wrapped to work on iOS and Android platforms. In order to define the gold standard regarding stool color, seven pediatri-


Abnormal colors
reference
Normal colors
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

- Cyclic epidemics of "Biliary Atresia" in newborn Australian livestock **(1964, 1988, 2007, 2013)**
- Coincide with maternal consumption of ***Dysphania plant*** (due to drought conditions)

**Time-space clustering**

*Lorent , Science Translational Medicine 7: Issue 286, pp. 286, 2015*

BILIARY ATRESIA

## Identification of a plant isoflavonoid that causes biliary atresia

Kristin Lorent,[1]* Weilong Gong,[1]* Kyung A. Koo,[2]* Orith Waisbourd-Zinman,[3,4] Sara Karjoo,[3] Xiao Zhao,[1] Ian Sealy,[5] Ross N. Kettleborough,[5] Derek L. Stemple,[5] Peter A. Windsor,[6] Stephen J. Whittaker,[7] John R. Porter,[2] Rebecca G. Wells,[1,8†] Michael Pack[1,9†]

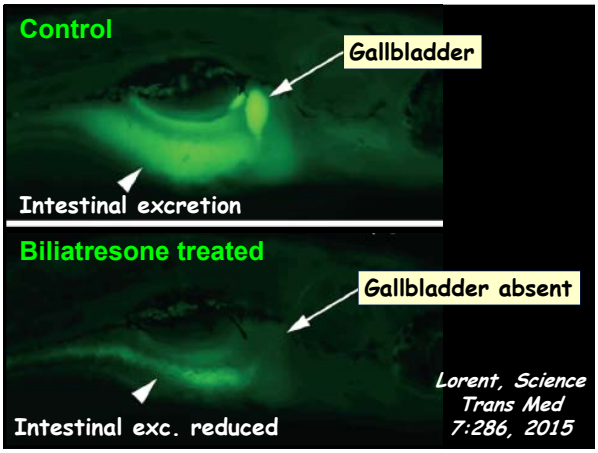
Biliary atresia (BA) is a rapidly progressive and destructive fibrotic disorder of unknown etiology affecting the extrahepatic biliary tree of neonates. Epidemiological studies suggest that an environmental factor, such as a virus or toxin, is the cause of the disease, although none have been definitively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

- **Imported *Dysphania* from pastures grazed on during the 2007 outbreak**

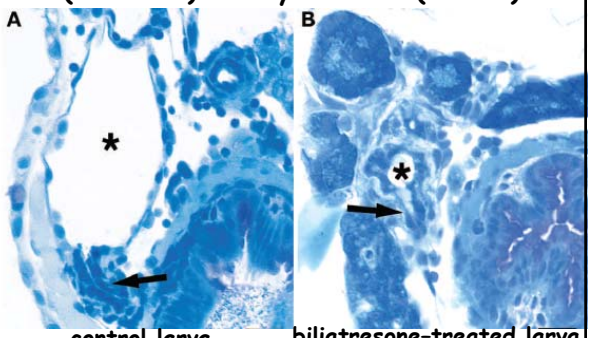
these findings provide direct evidence that BA could be initiated by perinatal exposure to an environmental toxin.

## 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**



Severe morphological defects of gallbladder (asterisks) and cystic duct (arrows)




*Lorent, Science Trans Med 7:286, 2015*

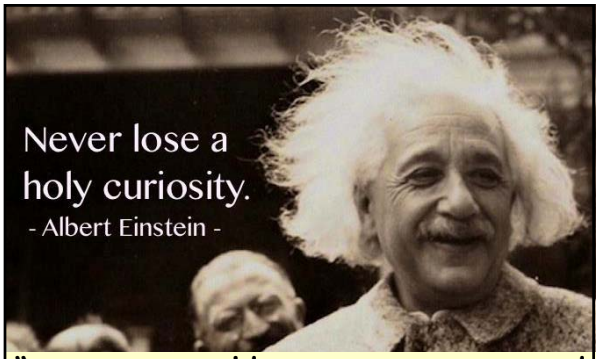
## Human biliary atresia initiated by perinatal exposure to a toxin?

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

*Lorent, ScienceTransMed 7:issue 286ra67, 2015*
*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"

"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