BRIGHAM AND WOMEN'S HOSPITAL

# Massachusetts ACP Meeting

# Update in Gastroenterology and Hepatology

## November 19th, 2016

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# Agenda

- Stomach and Small Bowel
  - Thromboembolism and GI bleeding after anticoagulants D/C
  - Sprue- a common problem
  - Bariatric surgery
- Colon
  - C. Difficile
  - Irritable Bowel Syndrome
  - Colonic Diverticular Diseases
- Liver
  - Nonalcoholic Liver Diseas

# The Risks of Thromboembolism Vs. Recurrent Gastrointestinal Bleeding After Interruption of Systemic Anticoagulation in Hospitalized Inpatients With Gastrointestinal Bleeding: A Prospective Study

Sengupta N, et al, Am J Gastro 2015; 110: 328-335

# Objective

- Anticoagulants carry a significant risk of gastrointestinal bleeding (GIB)

# Aim

- To determine the safety and risk of continuation of anticoagulation after GIB

# Methods

- A prospective observational cohort study was conducted on patients admitted to the hospital who had GIB while on systemic anticoagulation.
- Patients were classified into two groups at hospital discharge after GIB: those who resumed anticoagulation and those who had anti coagulation discontinued.

# Results

- 90 days after discharge the following outcomes were determined:
  - 197 patients who developed GIB while on systemic anticoagulation (n=145, 74% on warfarin)
  - During the follow-up period, 7 (4%) patients suffered a thrombotic event and 27 (14%) patients were readmitted for GIB
  - Anticoagulation continuation was independently associated on multivariate regression with a lower risk of major thrombotic episodes within 90 days.

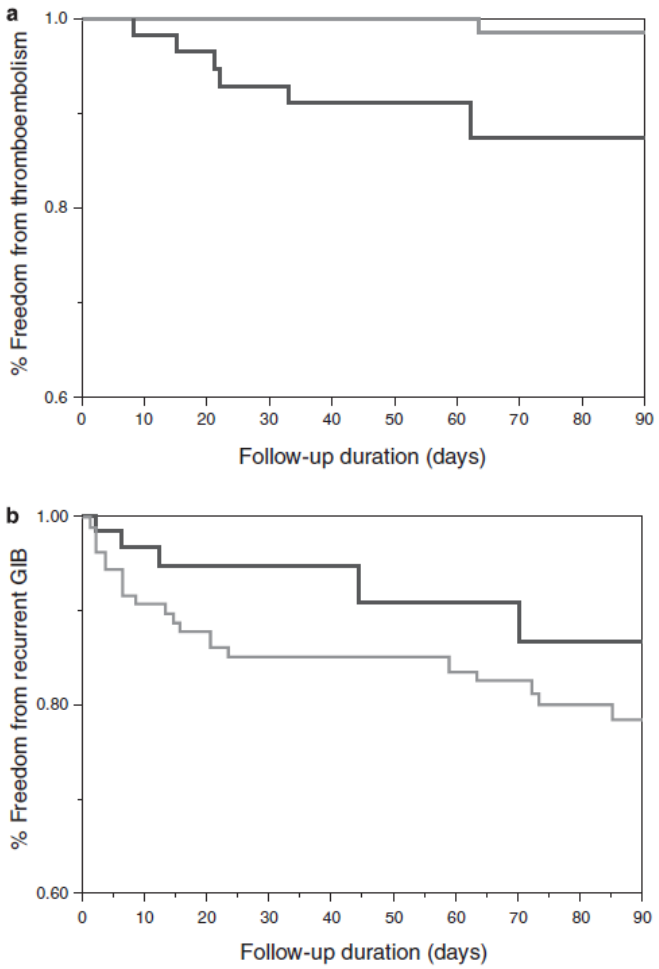



**Figure 1.** Time-to-outcome analysis according to resuming anticoagulation status. (**a**) Thrombosis ($P$=0.002, log-rank test) and (**b**) recurrent gastrointestinal tract bleeding (GIB; $P$=0.09, log-rank test). Gray, anticoagulation resumed; black, anticoagulation held.

*Sengupta N, et al, Am J Gastro 2015; 110: p. 334*

# Conclusions

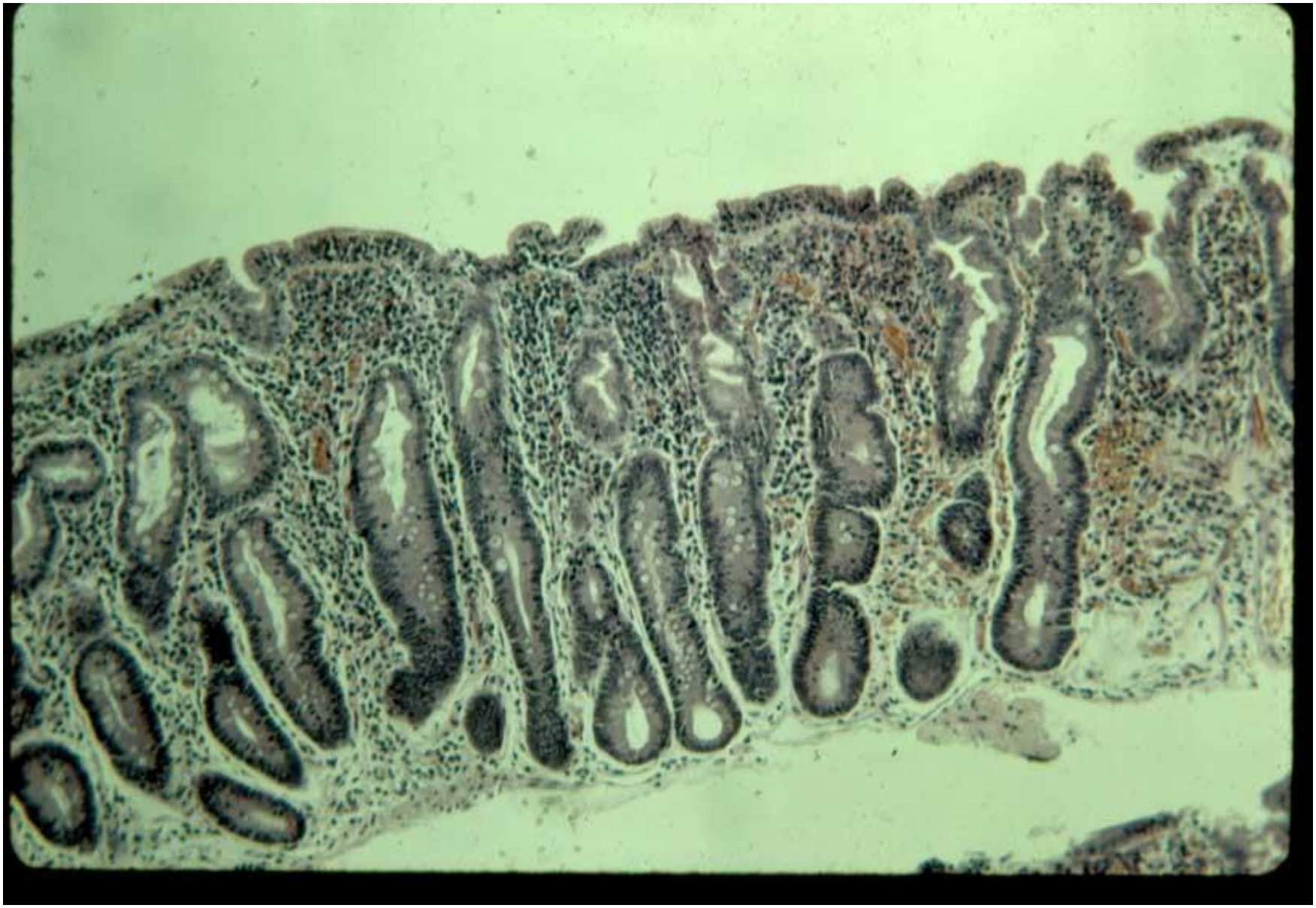
- Restarting anticoagulation at discharge after GIB was associated with fewer thromboembolic events without a significantly increased risk of recurrent GIB at 90 days
- The benefits of continuing anticoagulation at discharge may outweigh the risk of recurrent GIB.

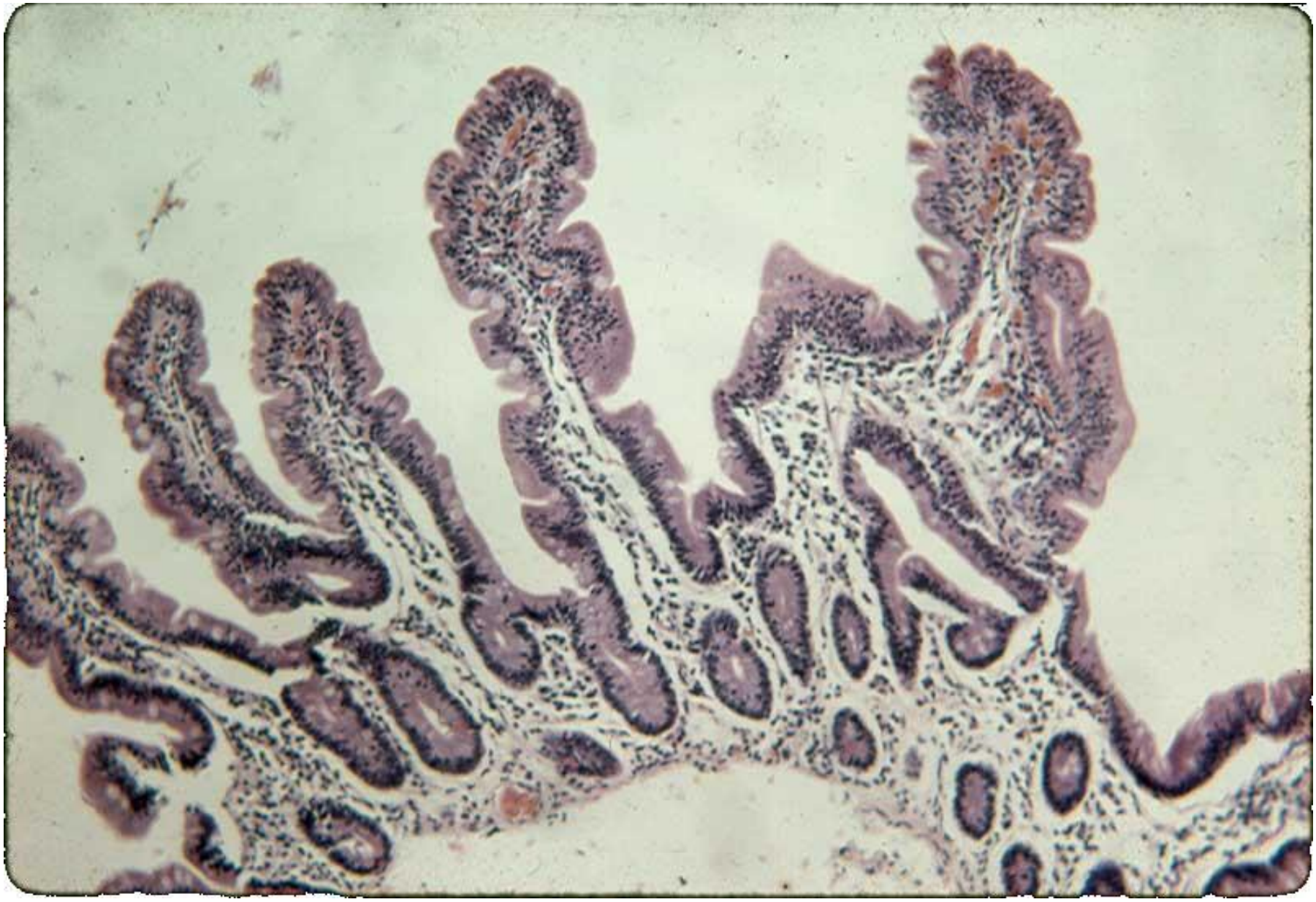
# Diagnosis of Celiac Sprue

1. Evidence of malabsorption (localized, generalized)
2. Abnormal small bowel biopsy (spectrum of changes)
3. Abnormal immunologic studies – 85-90% sensitivity 95% specificity
   - Anti-endomysial antibody
   - Tissue glutaminase antibody
4. Improvement with gluten-free diet (clinical, lab studies, histology)
5. Equivocal cases – gluten challenge

# The Many Faces of Celiac Sprue

- Classical presentation (diarrhea, weight-loss, malabsorption)
- Iron deficiency anemia (most common presentation)
- Metabolic bone disease
- Unexplained hypoalbuminemia
- Unexplained transaminitis
- “Diabetic diarrhea (5% $\Rightarrow$ celiac sprue)
- Small bowel biopsy $\Rightarrow$ intraepithelial lymphocytes (10% $\Rightarrow$ sprue)
- Asymptomatic elevation of serum transaminases (8% U.S. population)





# Celiac Disease: Things That Every Gastroenterologist and Internist Should Know

Oxentenko A.S. and Murray J.A.
Clinical Gastoenterology and Hepatology 2015; 13: 1396-1404

# Celiac Disease (CD) Pearls

- Patients with Celiac Disease should have all medications reviewed by a pharmacist to be sure they are gluten free
- B12 deficiency occurs in 12% of patients with Celiac Disease because of 1) Terminal ileal involvement; 2) autoimmune gastritis; and 3) pancreatic insufficiency
- Copper deficiency occurs in 6% of Celiac patients

# Celiac Disease (CD) Pearls

- Serologic titers of TTG IGA usually fall to normal by 2 years
- Histologic improvement is slow
  - 34% @ 2 years; 66% @ 5 years
  - 90% @ 9 years
- In patients with enteropathy on a gluten-free diet, CD can be excluded by absence of HLA DQ2 and DQ8

# 1

- The immunoglobulin A tissue transglutaminase is the single best serologic test to use for the detection of CD.

# 2

- Consider serologic testing of first-degree relatives, patients with type 1 diabetes mellitus, Down's, Turner's, and Williams' syndromes, as well as those with premature osteoporosis, iron deficiency, abnormal liver biochemistries, and other manifestations of CD.

# 3

- Patients already on a prolonged gluten-free diet (GFD) should be tested for the presence of HLA DQ2 or DQ8, thereby avoiding the need for further evaluation of CD in non-allelic carriers.

# 4

- The basic treatment of CD is a strict, lifelong GFD, enabled by an expert dietitian.

# 5

- Newly diagnosed adults with CD should be assessed for micronutrient deficiencies (iron, B12, folate, zinc, copper), fat soluble vitamin deficiencies (vitamin D), and bone densitometry.

# 6

- All patients diagnosed with CD should have clinical follow-up to ensure response and adherence to a GFD.

# 7

- In those with persistent or relapsing symptoms, the robustness of the original diagnosis should be reviewed, gluten exposure sought, and a systematic evaluation for alternative and associated diseases performed.

# 8

- Evaluate those with refractory disease for malignant transformation.

# Colon

- C. Difficile
- Irritable Bowel Syndrome

# Burden of Clostridium Difficile Infection in the United States

Lessa LC, et al, NEJM 2015; 372: 825-834

# Facts

- 15,461 cases of c.difficile infection identified in 10 geographic areas; 65.8% were health-care associated but only 24.2% had onset during hospitalization
- The estimated number of c.dificile infections in the us is 453,000
- Incidence is higher in females (1.26)
- Incidence is higher in whites (1.72)
- Incidence is higher in ages 65+ (8.65)
- The estimated number of first recurrences is 83,000 (18%)
- The estimated number of deaths is 29,300
- The NAP1Strain (most virulent) is 30.7% hospitalizations vs 18.8% community-acquired infections*

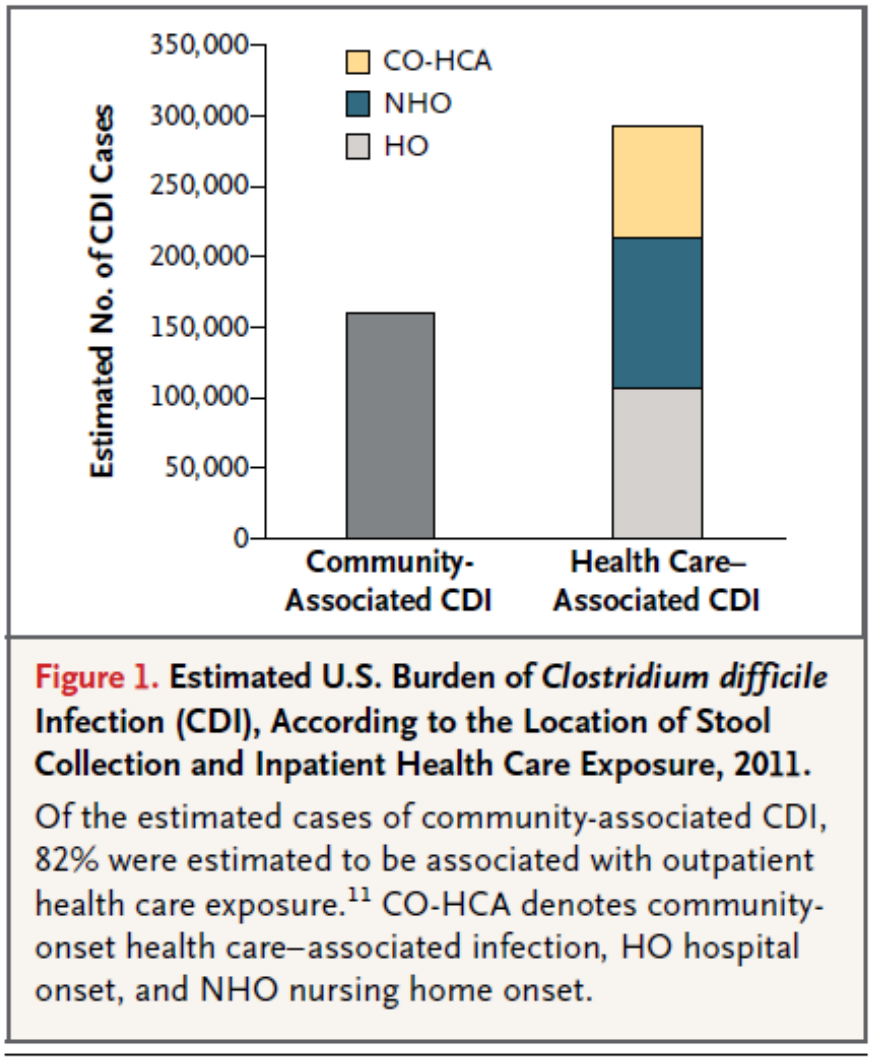



**Figure 1. Estimated U.S. Burden of *Clostridium difficile* Infection (CDI), According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.**

Of the estimated cases of community-associated CDI, 82% were estimated to be associated with outpatient health care exposure.[11] CO-HCA denotes community-onset health care–associated infection, HO hospital onset, and NHO nursing home onset.

*Lessa LC, et al, NEJM 2015; 372: p. 830*

# Colonization with Toxinogenic C. difficile upon hospital admission, and risk of infection: A systematic Review and Meta-Analysis

Zacharioudakis, IM et al. Am J Gastro 2015; 110:381-390

# Aim

- To study the association between the carriage of toxinogenic strains and ensuing c. difficile infections (CDIs)

# Results

- 19 out of 26,080 studies on 8,725 patients were included
- The pooled prevalence of toxinogenic C.difficile colonization was 8.1% with an increasing trend overtime.
- Patients colonized upon hospital admission had a 5.9 times higher risk of subsequent CDIs compared with noncolonized patients
- The risk of CDI for colonized patients was 21.8%, which was significantly higher than that of non colonized patients (3.4%)

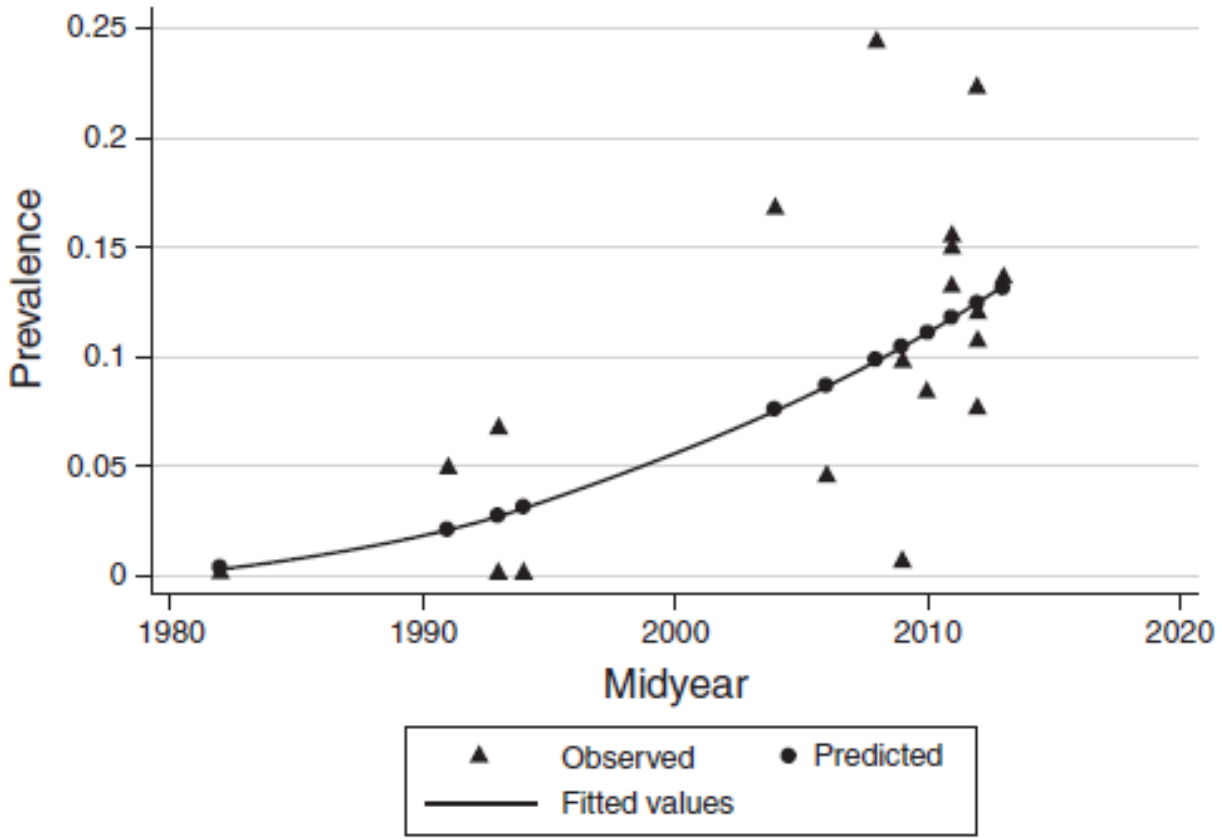



**Figure 2.** Toxinogenic *C. difficile* colonization trends over time. Observed (triangles) and fitted (circles) prevalence estimates, by study midyear.

Zacharioudakis, IM et al. Am J Gastro 2015;
110: p. 386

## Study Highlights

**WHAT IS CURRENT KNOWLEDGE**

- ✓ *C. difficile* infection is the most common healthcare-associated infection in the United States.
- ✓ The Centers for Disease Control and Prevention (CDC) characterized *C. difficile* as a pathogen that warrants urgent public health attention.
- ✓ The association between colonization with the toxinogenic *C. difficile* and subsequent infection is unknown.

**WHAT IS NEW HERE**

- ✓ Over 8% of patients admitted to the hospital are asymptomatic carriers of toxinogenic *C. difficile.*
- ✓ Colonized patients have an almost six times higher risk of infection compared with noncolonized patients.
- ✓ Patients hospitalized the previous 3 months have significantly higher risk to be colonized.

Zacharioudakis, IM et al. Am J Gastro 2015; 110: p. 389

# Conclusions

- Over 8% of admitted patients are carriers of the toxinogenic C. difficile with an almost 6 times higher risk of infection

# The Science, Evidence, and Practice of Dietary Interventions in Irritable Bowel Syndrome

Lacy, BE. Clin. Gastro. Hepatology 2015; 13: 1899-1906

# Background

- 60% to 70% of IBS patients report a worsening of symptoms after meals
- 50% to 70% report intolerance to various foods
- Food can cause GI symptoms.
  - Stimulation of mechanoreceptors and chemoreceptors
  - Alteration in GI transit
  - Alteration in intestinal osmolarity
  - Alteration in intestinal secretion

# Food Allergies

- Present in 1% to 4% of the US population but are not more prevalent in IBS patients.
- Food allergies can be classified as either IgE-mediated (type 1 hypersensitivity) or non–IgE-mediated. IgE-mediated rapid in onset (i.e. minutes)
  - peanuts, tree nuts, eggs, cow's milk, soy, fish, shellfish, strawberries, and wheat
  - GI symptoms include nausea, dysphagia, abdominal pain, vomiting, and diarrhea
- Non–IgE-mediated food allergies develop as a result of a cell-mediated response (T-helper 2 cells), are delayed in onset, present less acutely than IgE-mediated

# Food Intolerances

- Nonimmunologic events

**Table 1.** Etiology of Food Intolerances

| |
|---|
| Food chemicals or additives |
| Histamine, glutamate, caffeine, salicylates |
| Nonceliac gluten sensitivity |
| Enzyme defects |
| Lactase |
| Transport defects |
| Fructose |
| Sugar alcohols |
| Mannitol, sorbitol, xylitol, maltitol, erythritol |
| Excess fermentation |
| Short-chain carbohydrates |

# Food Intolerances

- Nonceliac gluten sensitivity
  - Ingestion of wheat in a patient without celiac disease or a wheat allergy
  - Prevalence estimated at 6%
  - (-) TTG antibodies
  - Normal small bowel biopsies
  - Improvement with gluten-free diet

# Food Intolerance

- Lactase deficiency
  - 30% Caucasians
  - 70% Asians
  - >70% African Americans
- Fructose Malabsorption
  - 50% of healthy volunteers had evidence of fructose malabsorption after 25g
  - 75% had malabsorption after 50g
  - Reference points: one 12oz of Coca Cola has 40g of fructose

# Food Intolerances

- Low FODMAPS diet
- (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols)
- High FODMAPS diet induces gas and GI symptoms in both IBS patients and healthy controls

# Food Intolerance

- Intestinal Permeability
- Increase in IBS patients who ingested gluten
- Increase in IBS patients challenged with wheat, soy, milk, eggs, and yeast

# Food Intolerance

- Small intestine bacterial overgrowth (SIBO)
- Symptoms are nonspecific and range from abdominal bloating and gas to diarrhea
- Accurate testing is problematic
- Lactulose breath test after 15g
  - Sensitivity 50-70%
  - Specificity <50%
- Note: Gut microbiome – $10^{i4}$ bacteria, 1000 species, millions of bacterial genes

# Specific Dietary Interventions for Irritable Bowel Syndrome

- Fiber Supplementation
  - Mechanism: colonic fermentation with production of short-chain fatty acids or its action as a prebiotic
  - Soluble fiber (psyllium) may be more effective than bran
- Elimination Diets
  - Helpful but not practical long-term

# Specific Dietary Interventions for Irritable Bowel Syndrome

- Very Low Carbohydrate Diet
  - 51% of calories were from fat, 45% were from proteins, and only 4% were from carbohydrates
  - Improvement in stool frequency and consistency

# Specific Dietary Interventions for Irritable Bowel Syndrome

- Low Fructose/Fructan Diet
  - 1 study of 62 patients
    - 75% noted decrease in gas, bloating, abdominal pain, and diarrhea
  - 1 study of 31 patients
    - 71% noticed decrease in abdominal pain, bloating, and diarrhea vs. baseline

# Specific Dietary Interventions for Irritable Bowel Syndrome

- Low-/No-Gluten Diet
  - 34 patients
  - Gluten 16 g/d or no gluten
  - 68% on gluten
  - 40% on placebo
  - Increase in symptoms of abdominal pain, bloating
- 45 patients IBSD
  - Stool frequency was reduced in patients randomized to the gluten-free diet (P ¼ .04), and these effects were more evident in those who were HLA-DQ2 or HLA-DQ8 positive

# Specific Dietary Interventions for Irritable Bowel Syndrome

- Low FODMAPs Diet
  - 41 I.B.S. patients
  - 4 weeks usual diet
  - 4 weeks low FODMAPs
- Decreased IBS symptoms
- Decreased stool frequency
- 90 I.B.S. patients
  - Decrease in symptoms 75% - especially those with a positive fructose breath test

# Colonic Myochosis As A Cause of Recurrent LLQ Abdominal Pain

Myochosis:

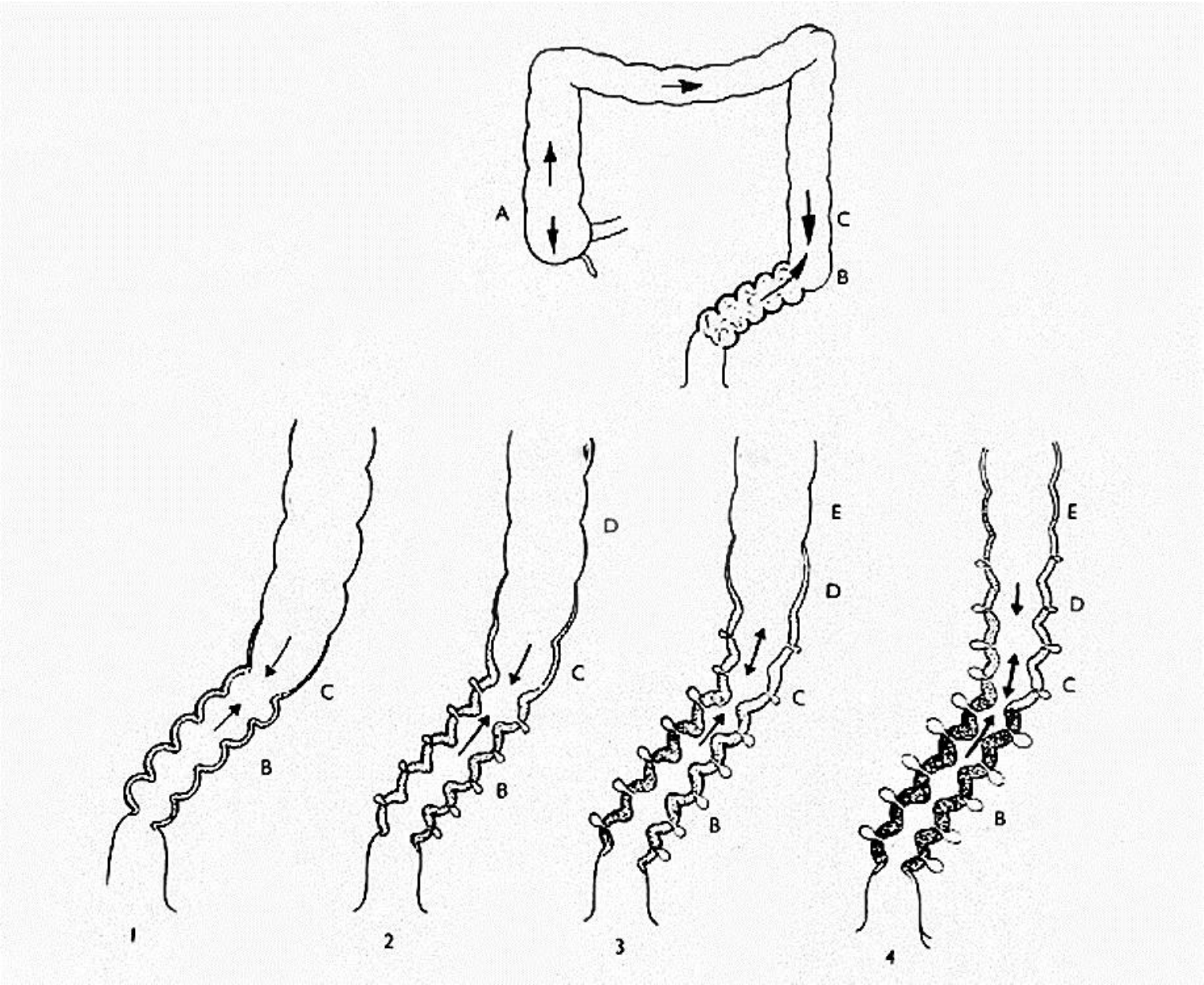
- Thickening of the circular and longitudinal muscles especially the sigmoid and left colon.

Clinical Features:

- Recurrent LLQ abdominal pain
- Thin stools (pencil-like)
- Palpable LF colon, often thickened
- Colonoscopy – usually not helpful
- Ba enema – infrequently done

Treatment:

- bulking agents (Benefiber, Metamucil, etc.)
- Tablets – can ↑ and tolerate dosage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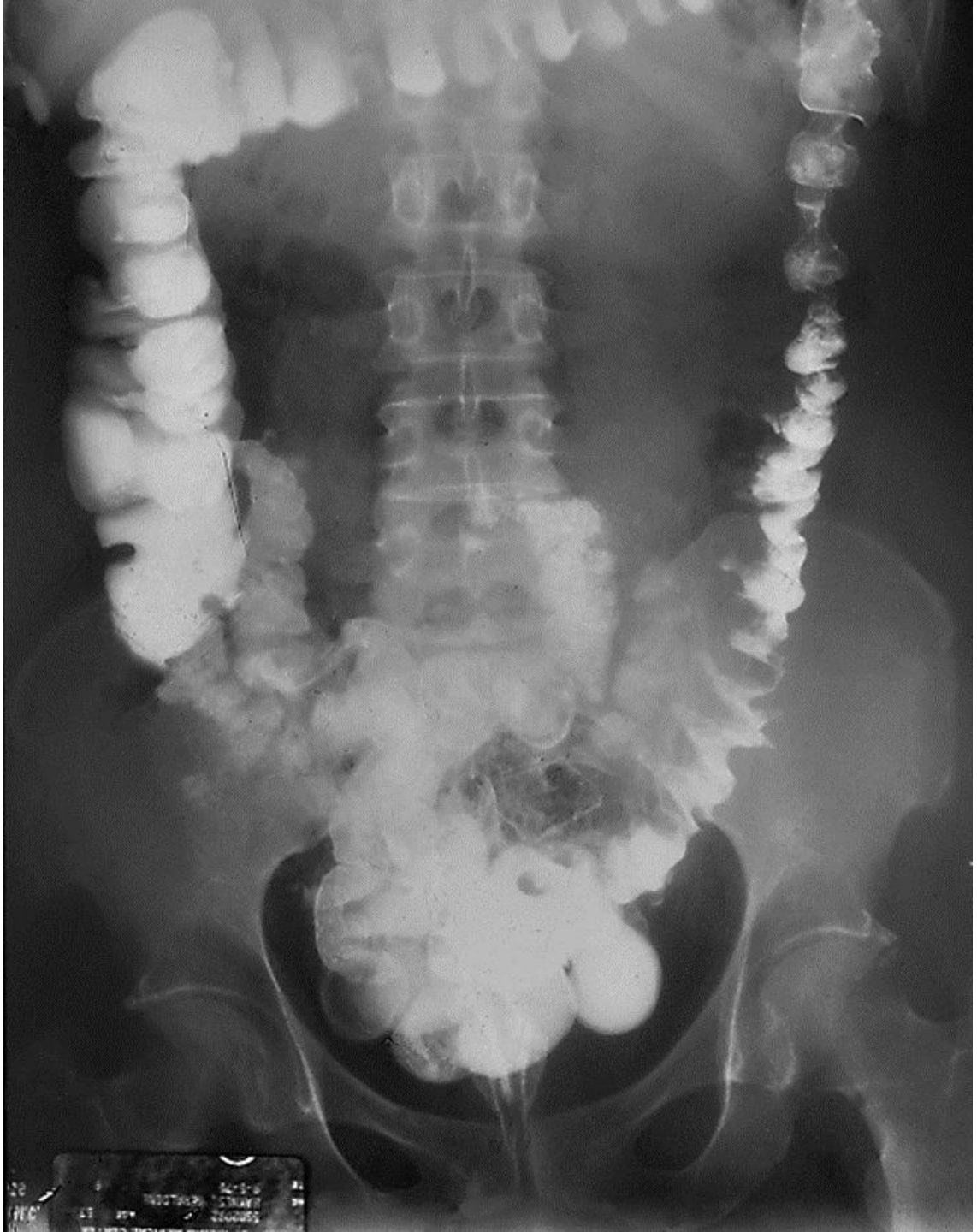

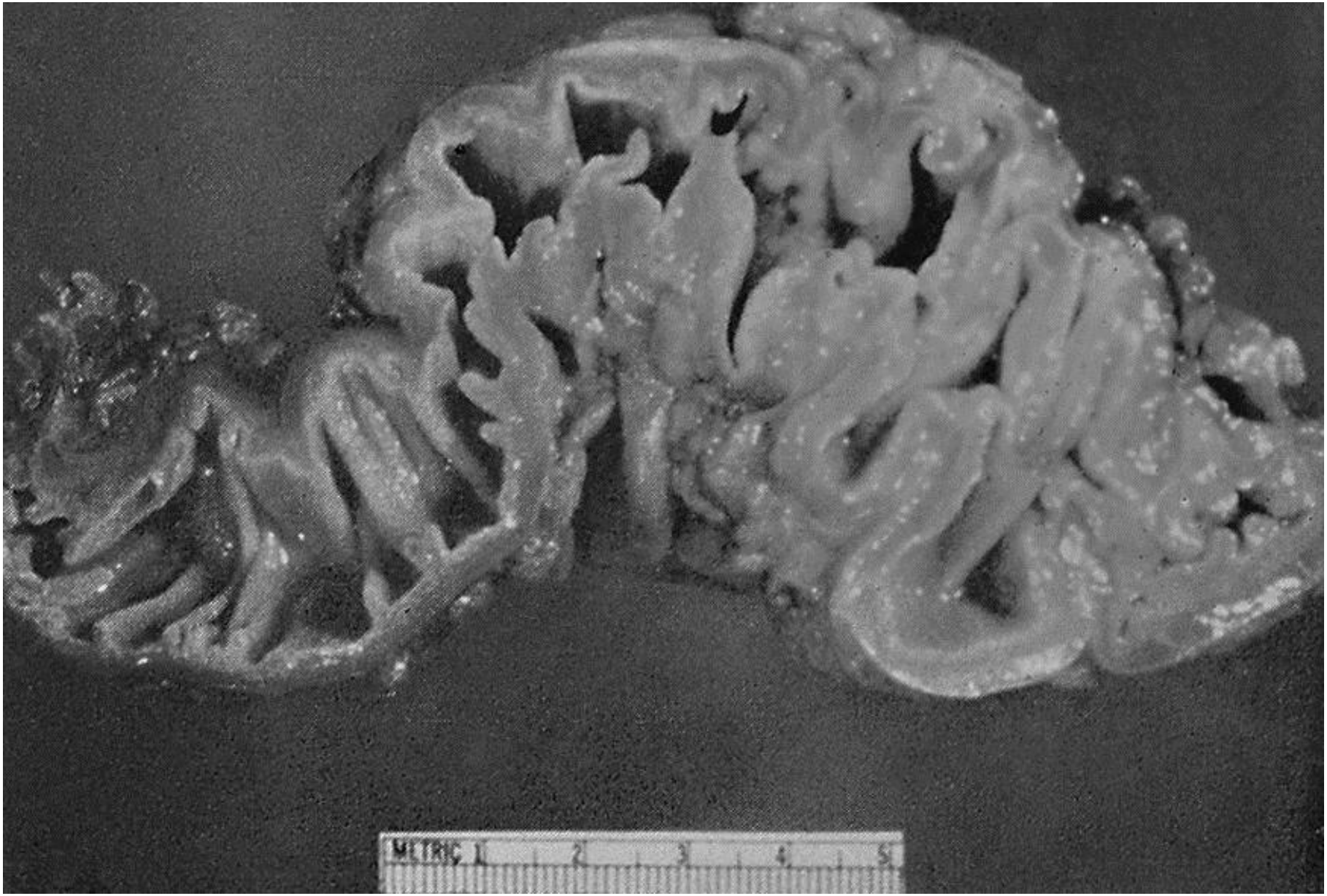
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# Liver

- Nonalcoholic Fatty Liver Disease (NAFLD)

# Nonalcoholic Fatty Liver Disease
# A Systematic Review

Rinella ME. JAMA 2015; 313: 2263-2273

# Aim:

- To identify patients with nonalcoholic fatty liver disease at greatest risk of nonalcoholic steatohepatitis and cirrhosis; to discuss the role and limitations of current diagnostics and liver biopsy to diagnose nonalcoholic steatohepatitis; and to provide an outline for the management of patients across the spectrum of nonalcoholic fatty liver disease.

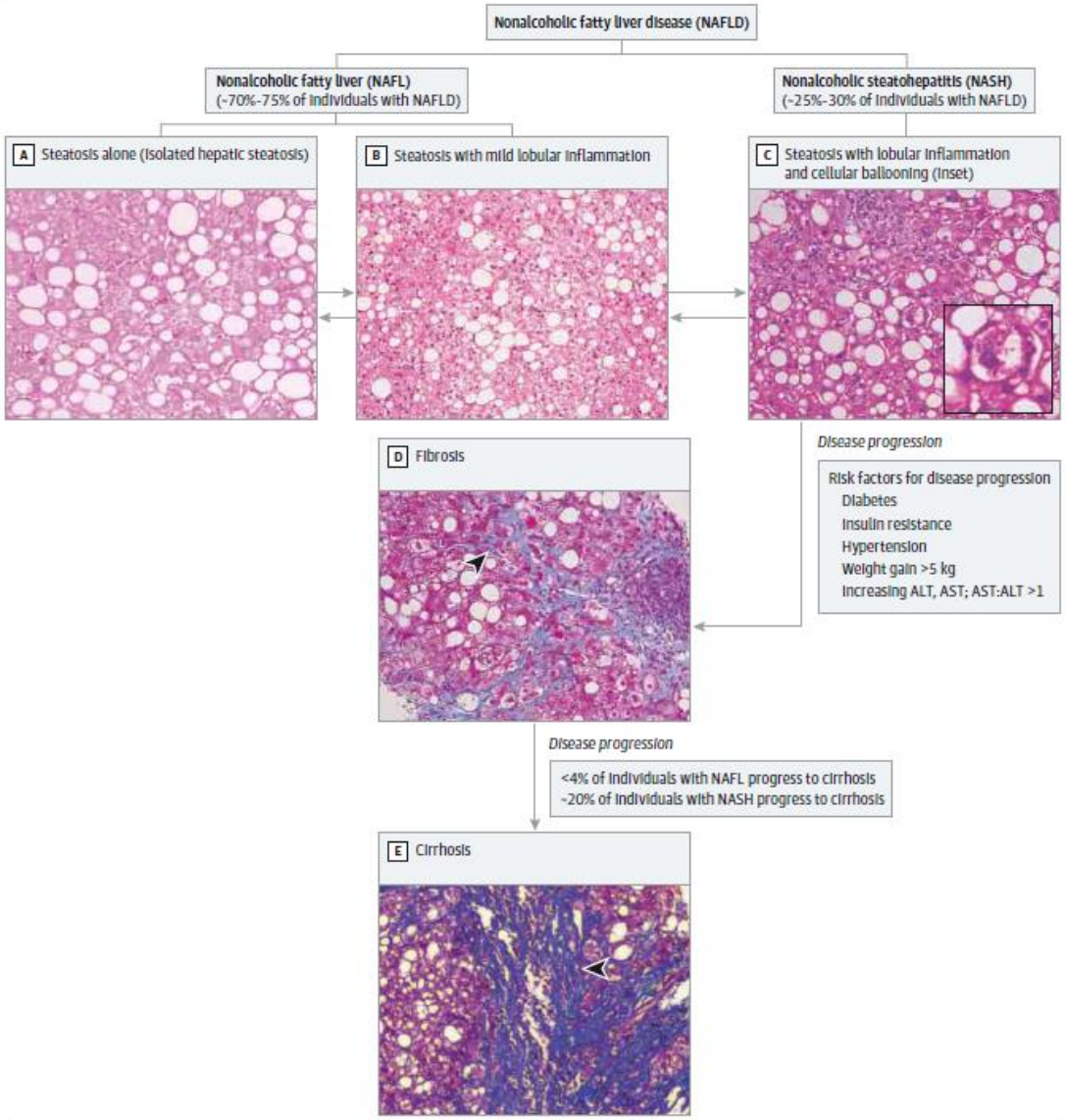
# Results

- Sixty-six percent of patients older than 50 years with diabetes or obesity are thought to have nonalcoholic steatohepatitis with advanced fibrosis.

# Conclusion

- Between 75 million and 100 million individuals in the United States are estimated to have nonalcoholic fatty liver disease and its potential morbidity extends beyond the liver.

Figure 1. Histological Subtypes of NAFLD and Their Implications for Disease Progression




Nonalcoholic fatty liver disease is broadly divided into those with NAFL (isolated steatosis with or without nonspecific inflammation) and NASH, with varying degrees of hepatic fibrosis. A, Isolated steatosis characterized by macrovesicular fatty change in the absence of cellular injury (ballooning) (hematoxylin-eosin, original magnification × 10). B, Steatosis with nonspecific inflammation (hematoxylin-eosin, original magnification × 20). C, NASH characterized by the additional presence of cellular ballooning (inset) (hematoxylin-eosin, original magnification × 20). D, NASH with early fibrosis in a typical pericellular pattern (arrowhead) (Trichrome, original magnification × 20). E, NASH cirrhosis characterized by the development of broad collagen bands that form nodules (arrowhead) (Trichrome, original magnification × 10). Other characteristic features of NASH may or may not be present once cirrhosis has developed. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; AST:ALT, ratio of AST to ALT.

Rinella ME. JAMA 2015; 313: 2263-2273

## Box 1. Established Risk Factors Associated With Nonalcoholic Steatohepatitis and More Progressive Disease

**Risk Factors**

- Obesity (central)
- Hypertension
- Dyslipidemia
- Type 2 diabetes
- Metabolic syndrome

**Adult Treatment Panel III Definition of the Metabolic Syndrome**[13]

Patient must have 3 or more of the following:

- Waist circumference of greater than 102 cm in men and greater than 88 cm in women
- Level of triglycerides of 150 mg/dL or greater
- High-density lipoprotein cholesterol level of less than 40 mg/dL in men and less than 50 mg/dL in women
- Systolic blood pressure of 130 mm Hg or greater or diastolic blood pressure of 85 mm Hg
- Fasting plasma glucose level of 110 mg/dL or greater

Rinella ME. JAMA 2015; 313: 2263-2273

# Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients

Lassailly, et al. Gastroenterology 2015; 149: 379-386

# Aim:

- To determine the biological and clinical effects of bariatric surgery in patients with NASH.

# Methods

- From May 1994 through May 2013, 109 morbidly obese patients with biopsy-proven NASH underwent bariatric surgery at the University Hospital of Lille, France (the Lille Bariatric Cohort).

# Conclusions

- Bariatric surgery induced the disappearance of NASH from nearly 85% of patients and reduced the pathologic features of the disease after 1 year of follow-up.
- It could be a therapeutic option for appropriate morbidly obese patients with NASH who do not respond to lifestyle modifications.
- More studies are needed to determine the long-term effects of bariatric surgery in morbidly obese patients with NASH.