Celiac Disease in Children

Ivor Hill, MD
Professor of Clinical Pediatrics
The Ohio State University College of Medicine
Section Chief, Gastroenterology and
Director, Celiac Clinic
Nationwide Children's Hospital

Disclosure

I have no relevant financial relationships with the manufacturers of any commercial products and/or provider of commercial services discussed in this CME activity.

I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.

Celiac Disease

Celiac Disease Facts

- **Affects ~ 1% of the USA population***
- **2-3 million cases in the USA**
- **5-20 affected children in average practice**
- **~ 80% undiagnosed**

***Arch Int Med 2003;163:286-92**

- Med 2003;163:286-92

Celiac Disease Learning Objectives

Identify children in need of testing for celiac disease

Choose most effective serological tests for screening

Understand the need to confirm the diagnosis before treating.

Celiac Disease Guidelines: 2004-2013

Celiac Disease Guidelines

- Who to test?
- How to test?
- How to Treat?

Celiac Disease Guidelines

Who to test?

Celiac Disease Guidelines

Who to test?

Symptomatic
- **"typical" – first line test**
- **"less typical" - consider**

Celiac Disease Guidelines

Who to test?

Symptomatic
- "typical" – first line test
- "less typical" - consider

What Symptoms are associated with celiac disease?

Symptomatic CD

Symptoms in children

Highly variable
- age of onset
- severity of symptoms
- single or combined

Symptomatic CD

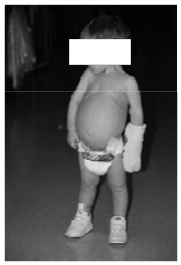
Symptoms in children

Highly variable
- **age of onset**
- **severity of symptoms**
- **single or combined**

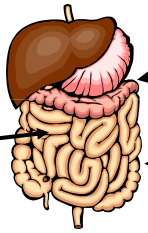
Symptoms mainly GI in young children. Non-GI sxs more common later.

Celiac Disease

- **Symptomatic group**
  - **Gastrointestinal – early onset**
  - **Age – 6 mths – 2 yrs**



Abdominal distention



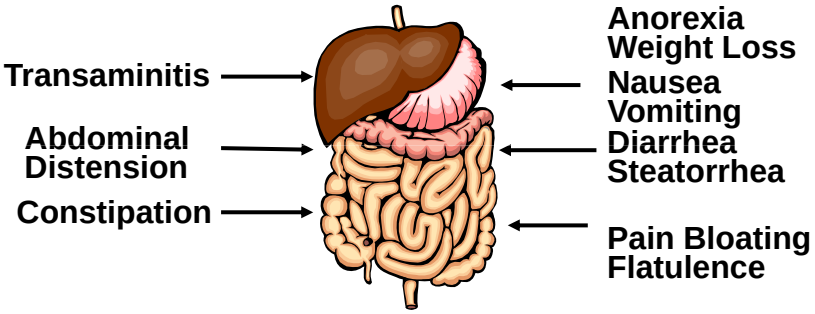
Anorexia
Weight loss
Wasting

Crisis!

Diarrhea
Steatorrhea

Celiac Disease

- **Symptomatic group**
  - Gastrointestinal – late onset
  - Age – childhood to young adult

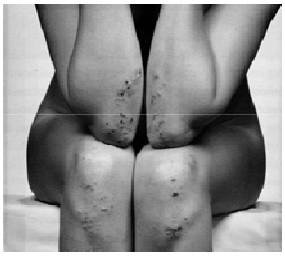


Celiac Disease

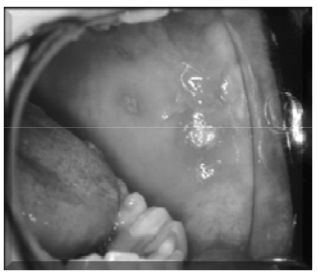
Symptomatic group
Non-Gastrointestinal

Skin and mucous membranes

Dermatitis herpetiformis



Aphthous ulcers

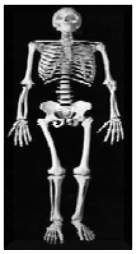


Celiac Disease

Symptomatic group
Non-Gastrointestinal

Musculoskeletal system

Short stature

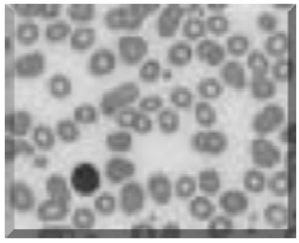


Rickets
Osteopenia
Osteoporosis
Arthritis
Fractures

Celiac Disease

Symptomatic group
Non-Gastrointestinal

Hematological system



Anemia
- **iron deficiency**
- **folate/B12**

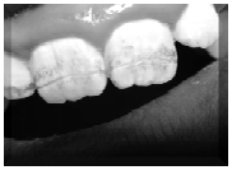
Leukopenia

Bruising/bleeding
- **vitamin K deficiency**
- **platelet dysfunction**

Celiac Disease

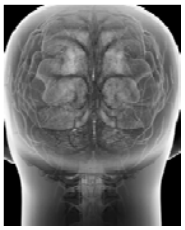
Symptomatic group
Non-Gastrointestinal

Miscellaneous



Dental enamel hypoplasia

Reproductive system
- **pubertal delay**
- **infertility**
- **recurrent abortions**
- **low birth weight**



Central nervous system
- **behavioral changes**
- **anxiety disorders**
- **learning difficulties**

Celiac Disease

Asymptomatic group
- **At risk for CD**

Celiac Disease

Asymptomatic group
- At risk for CD

Autoimmune
- Type 1 DM
- Thyroiditis
- A.I. Hepatitis
- Sjogren's
- Arthritis

Celiac Disease

Asymptomatic group
- At risk for CD

Autoimmune
- Type 1 DM
- Thyroiditis
- A.I. Hepatitis
- Sjogren's
- Arthritis

Non-autoimmune
- Relatives
- Down syndrome
- Turner syndrome
- Williams syndrome
- IgA deficiency

Celiac Disease Guidelines

Who to test?

Symptomatic
- **"typical" – first line test**
- **"less typical" - consider**

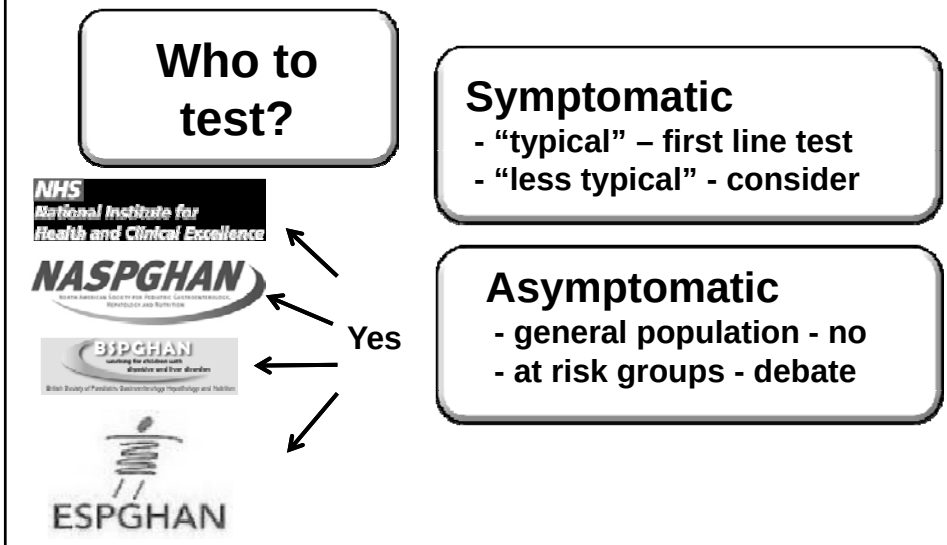
Celiac Disease Guidelines

Who to test?

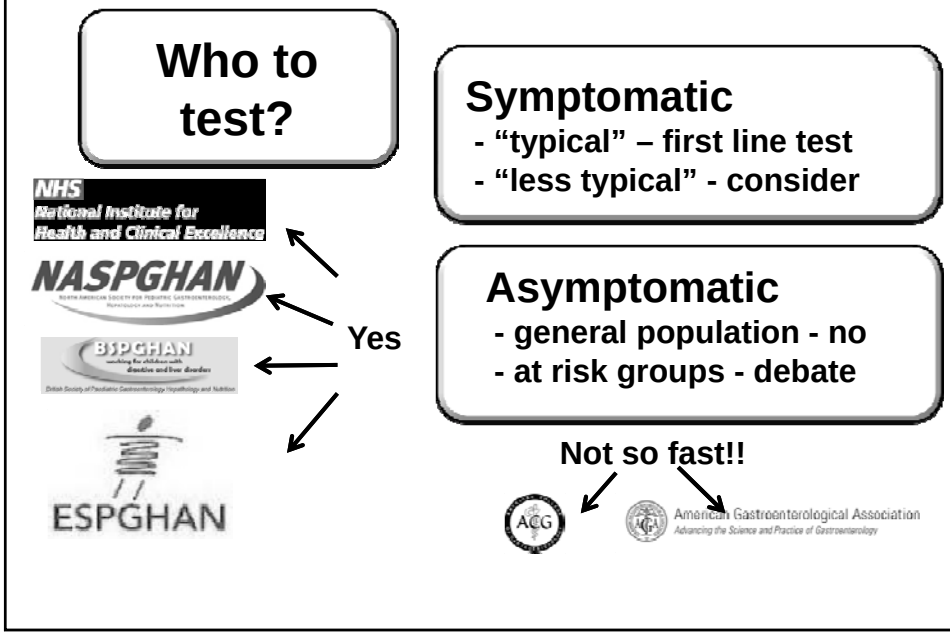
Symptomatic
- **"typical" – first line test**
- **"less typical" - consider**

Asymptomatic
- **general population - no**
- **at risk groups - debate**

Celiac Disease Guidelines



Celiac Disease Guidelines



Celiac Disease

Testing the Asymptomatic Debate

Celiac Disease

Testing the Asymptomatic Debate

Protagonists!
Increased mortality
Increased malignancies
Other morbidities – bones, growth, other AID's

Celiac Disease

Testing the Asymptomatic Debate

Protagonists!
Increased mortality
Increased malignancies
Other morbidities – bones, growth, other AID's

Antagonists!
Natural history unknown
Benefits - uncertain
Compliance -poor
QOL issues

Celiac Disease Guidelines

Who to test?

How to test?

How to Treat?

Celiac Disease

Commercially available tests

- Antigliadin – IgA AGA & IgG AGA
- Transglutaminase – IgA tTG (IgG tTG)
- Endomysium – IgA EMA (IgG EMA)
- Deamidated gliadin – IgA DGP & IgG DGP

Test	Sensitivity (percent)	Specificity (percent)	Tech-nology	Cost
IgA AGA	80 (52-100)	85 (47-100)	Low	$
IgG AGA	80 (42-100)	80 (47-94)	Low	$
IgA tTG	95 (86-100)	96 (90-98)	Low	$$*
IgA EMA	90 (86-100)	98 (94-100)	High	$$$$+
IgA DGP	88 (74-100)	90 (80-95)	Low	$$#
IgG DGP	80 (70-95)	98 (90-100)	Low	$$#

Gastroenterology 2005;128:S25.
JPGN 2012;54:229-241

Am J Gastroenterol 2010;105:2520-2524.

Recommended Testing for Celiac Disease.

Test	Sensitivity (percent)*	Specificity (percent)*	Tech-nology	Cost
~~IgA AGA~~	~~52-100~~	~~47-100~~	~~Low~~	~~$~~
~~IgG AGA~~	~~42-100~~	~~47-94~~	~~Low~~	~~$~~
IgA tTG	95	96	Low	$$
IgA EMA	90	98	High	$$$$
IgA DGP	88	90	Low	$$
IgG DGP	80	98	Low	$$

Recommended Testing for Celiac Disease.

Test	Sensitivity (percent)*	Specificity (percent)*	Tech	
~~IgA AGA~~	~~52-100~~			
~~IgG AGA~~	~~42~~			
IgA				$$
			High	$$$$
		90	Low	$$
Ig	80	98	Low	$$

Most reliable and cost effective single test
Need to know serum IgA level?

Celiac Disease
Special Considerations

IgA deficiency
- **IgG (tTG, EMA or DGP)**
- **consider biopsy**

Celiac Disease
Special Considerations

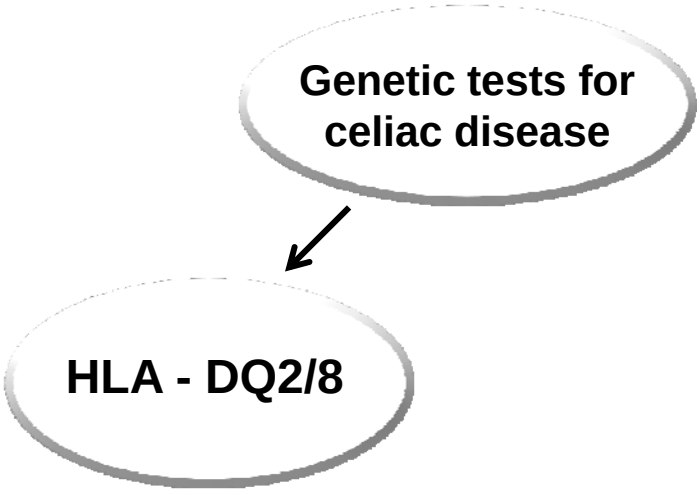
IgA deficiency
- **IgG (tTG, EMA or DGP)**
- **consider biopsy**

The young child (< 2 yrs)
- **tTG IgA + DGP IgG (ESPGHAN)**

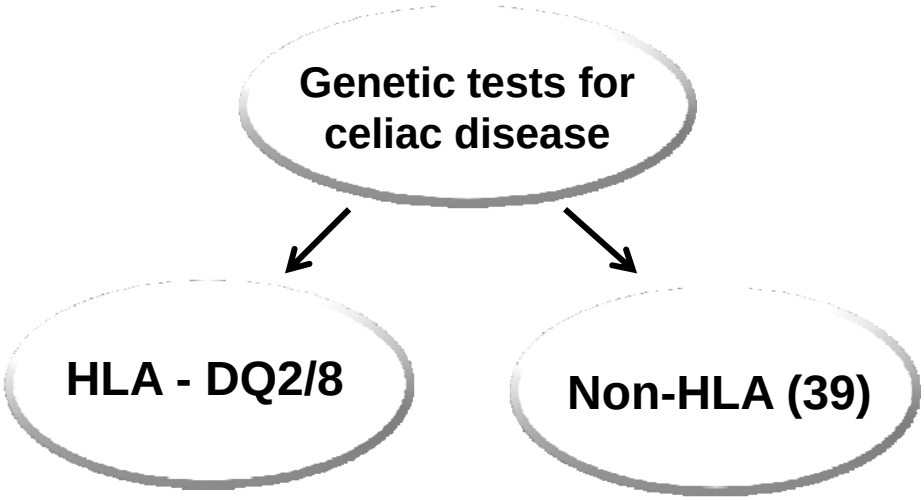
Celiac Disease

Genetic tests for celiac disease

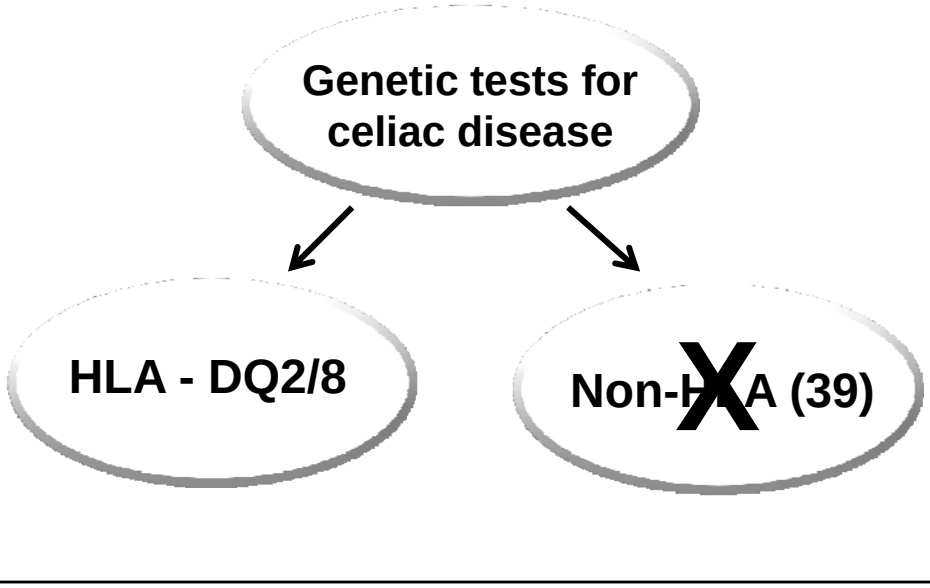
Celiac Disease



Celiac Disease



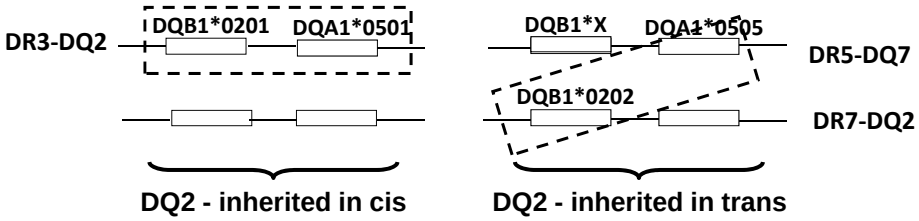
Celiac Disease



Celiac Disease

HLA genes in celiac disease

- **DQ2 > 95% of celiac individuals**
  20% -30% general population
- **DQ8 majority of non DQ2 cases**

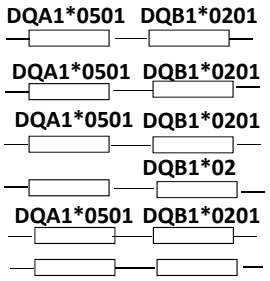


Celiac Disease

The Gene Dose Effect*

Relative risk

- **DQ2 homozygous**
- **DQ2 + DQB1*02**
- **DQ2 + DQ/X**



- Increased peptide binding & gluten specific T cell response #

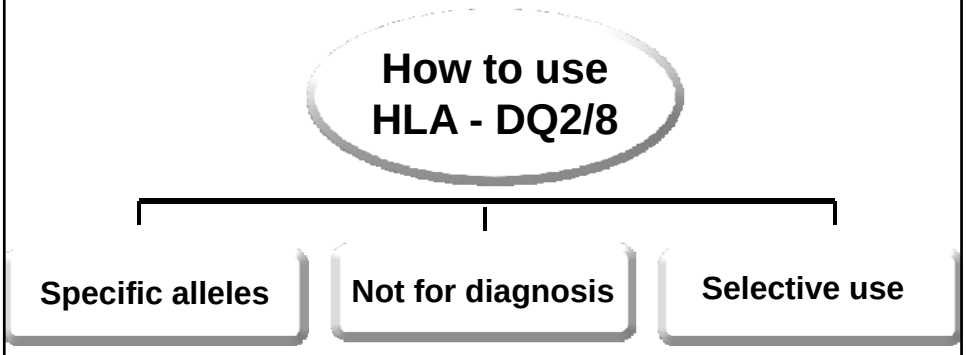
*** Greco L, et al. Frontiers in celiac disease. Karger 2008;12:46-56.**

 # Vader W, et al, PNAS 2003;100:12390-12395.

Celiac Disease

- Non DQ2 and/or DQ8 celiac
  - European collaborative study#
  - 1008 biopsy confirmed cases
  - 61 negative for DQ2 and/or DQ8
  - 57 positive for half the DQ2 heterodimer
    - 41 – DQB1*02
    - 16 – DQA1*05

Celiac Disease



Definitive Testing

Celiac Disease

Is a biopsy needed in all cases?

NASPGHAN

American Gastroenterological Association
Advancing the Science and Practice of Gastroenterology

ACG

ESPGHAN

Definitive Testing

Celiac Disease

Is a biopsy needed in all cases?

NASPGHAN - **Yes**

American Gastroenterological Association
Advancing the Science and Practice of Gastroenterology - **Yes**

ACG - **Yes**

ESPGHAN - **No**

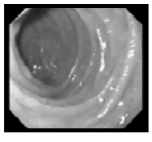
Celiac Disease and Beyond

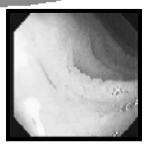
Biopsy Consensus Points

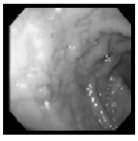
Celiac Disease and Beyond

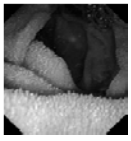
Biopsy Consensus Points

Endoscopic


Normal


Scalloping


Nodularity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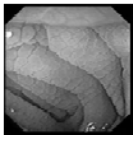
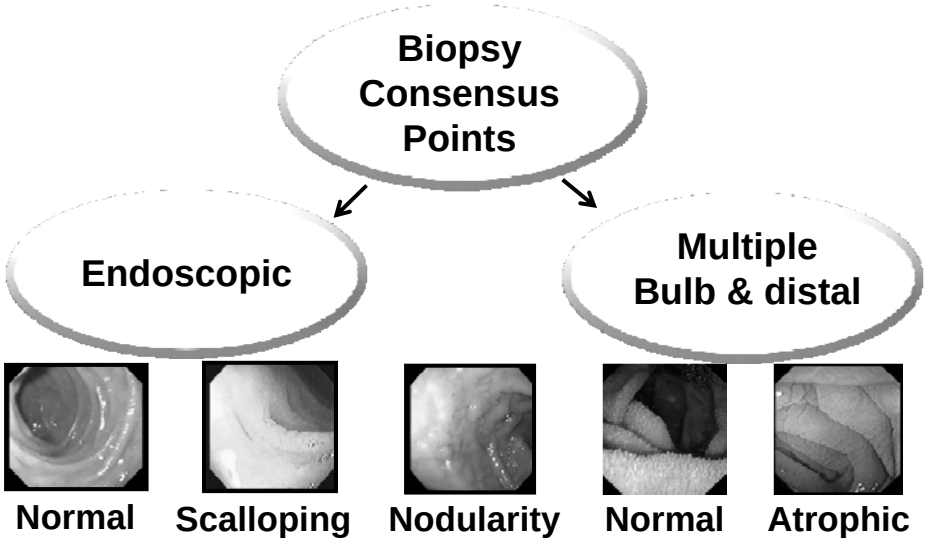
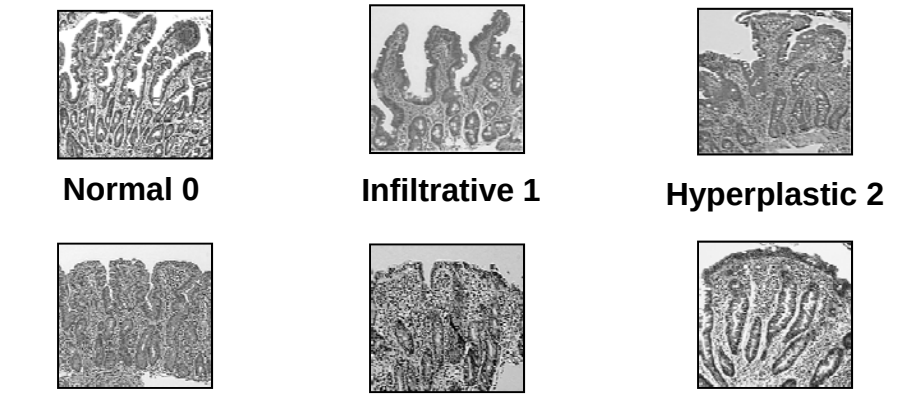

Atrophic

Celiac Disease and Beyond



Celiac Disease

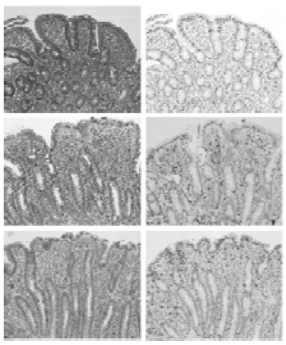


Marsh MN. Scanning Microsc. 1988;2:1663-84.

Celiac Disease

Confirming the Dx

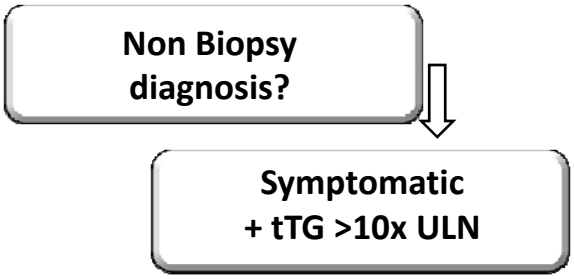
- **Marsh III – strong**
- **Marsh II – moderate**
- **Marsh I – weak**



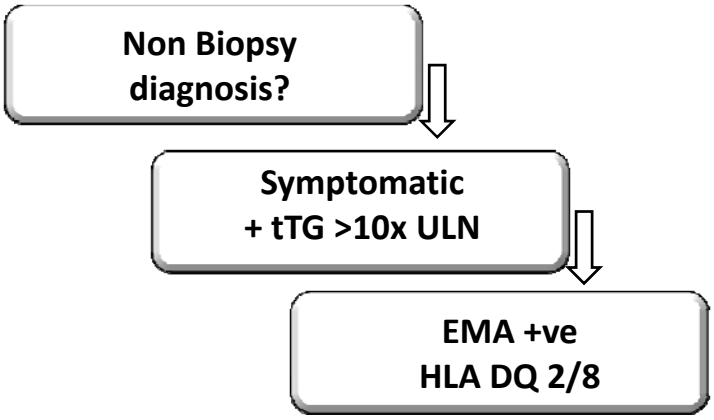
Celiac Disease

- **Non Biopsy diagnosis?**

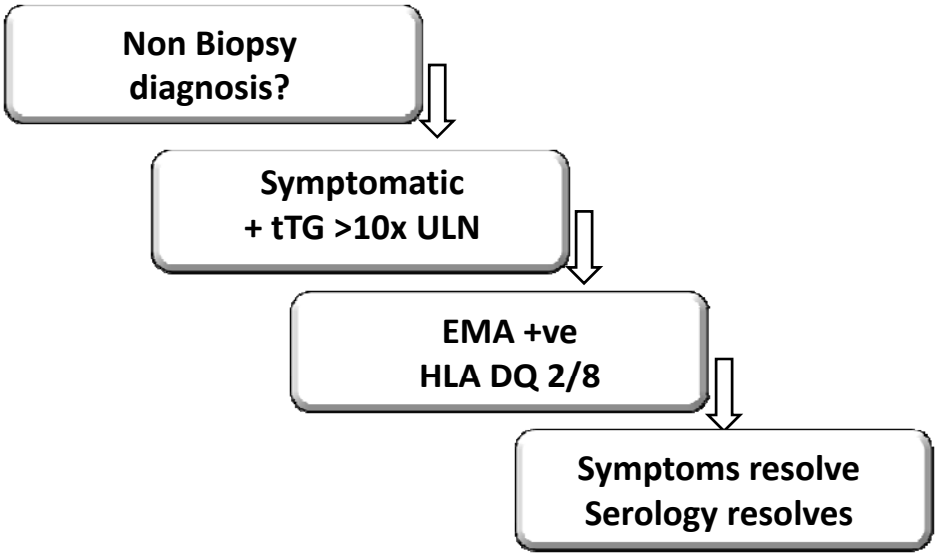
Celiac Disease



Celiac Disease



Celiac Disease



Celiac Disease

- **Recommendation 3.4.1.**
  - **Every antibody test must be validated in a paediatric population of at least 50 children with active CD and 100 control children……**
  - **Laboratories providing CD antibody test results should participate continuously in quality control programs at a national or European level.**

Celiac Disease

Confirming the Dx

Comparison of Commercially Available Serologic Kits for the Detection of Celiac Disease

Afzal J. Naiyer, MD, Lincoln Hernandez, MD, Edward J. Ciaccio, PhD, Konstantinos Papadakis, MD, John S. Manavalan, MD, Govind Bhagat, MD, and Peter H. R. Green, MD

(J Clin Gastroenterol 2009;43:225–232)

Sensitivity - 71.4 – 96.4%
Specificity - 87.5 – 100%
False + ve - 13 -25%

Clinical Chemistry 50:11 2135–2135 (2004)

Clinical Immunology

Diagnostic Accuracy of Ten Second-Generation (Human) Tissue Transglutaminase Antibody Assays in Celiac Disease

Britta Van Meensel,[1] Martin Hiele,[2] Ilse Hoffman,[2] Severine Vermeire,[2] Paul Rutgeerts,[2] Karel Geboes,[4] and Xavier Bossuyt[2*]

Celiac Disease

Confirming the Dx

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Need for Standardization!

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Celiac Disease

Confirming the Dx

Clin Gastroenterol Hepatol. 2012 Oct 25. pii: S1542-3565(12)01280-3. doi: 10.1016/j.cgh.2012.10.025. [Epub ahead of print]

Defining Thresholds of Antibody Levels Improves Diagnosis of Celiac Disease.

Vermeersch P, Geboes K, Mariën G, Hoffman I, Hiele M, Bossuyt X.

Laboratory Medicine, Immunology, University Hospitals Leuven, Catholic University of Leuven, Belgium.

Abstract

BACKGROUND & AIMS: The European Society for Pediatric Gastroenterology and Nutrition proposed guidelines for the **diagnosis** of **celiac disease**, stating that duodenal biopsy is no longer needed if patients have symptoms and **levels** of immunoglobulin A anti-tissue transglutaminase (IgA anti-tTG) more than 10-fold the cutoff value. We evaluated the accuracy of this guideline in a well-characterized population using different commercial assays.

METHODS: We analyzed **levels** of IgA anti-tTG in serum samples from 104 consecutive pediatric and adult patients who were not deficient in IgA and diagnosed with **celiac disease** from August 1, 2000 to December 31, 2009. We also analyzed serum samples from 537 consecutive patients without **celiac disease** (controls), collected from May 1, 2004 to October 12, 2006, who underwent intestinal biopsy analysis. Serum **levels** of antibodies were quantified using assays from BioRad, INOVA, Genesis, and Thermo Fisher.

RESULTS: The likelihood ratio (probability of a specific result in patients divided by probability of the same result in controls) for **celiac disease** increased with **levels** of IgA anti-tTG in all assays. Depending on the assay, the likelihood ratio for **levels** >10-fold the cutoff ranged from 111 to 294. The percentage of patients with **celiac disease** with **levels** of IgA anti-tTG>10-fold the cutoff ranged from 41% to 61%, depending on the assay. For **levels** of anti-tTG>10-fold the cutoff, the post-test probabilities for **celiac disease** (probability of **disease**, based on pre-test probability and test result) were, depending on the assay, 89%-96% and 53%-75% (depending on the assay), for pre-test probabilities (probability of **disease** depending on symptoms) of 7% and 1%, respectively.

CONCLUSIONS: To **diagnosis celiac disease** based on serologic factors, it might be best to define **thresholds** for **levels** of IgA anti-tTG based on a predefined likelihood ratio or post-test probability, instead of a multiple of a cutoff value. Patients with a high pre-test probability and **levels** of anti-tTG >10-fold the cutoff have a high probability for having **celiac disease**, aiding clinical decision making.

Celiac Disease

Confirming the Dx

SHORT COMMUNICATION

ESPGHAN Guidance on Coeliac Disease 2012: Multiples of ULN for Decision Making Do Not Harmonise Assay Performance Across Centres

*William Egner, †Anna Shrimpton, †Ravishankar Sargur, *Dina Patel, and †Kirsty Swallow

ABSTRACT

The updated ESPGHAN guidance on coeliac disease recommends the use of common multiples of the upper limit of normal (ULN) for IgA tissue transglutaminase antibodies (TG2) when deciding which diagnostic pathway to follow. The current lack of standardisation between assays makes it difficult to harmonise results between centres as different performance characteristics are observed with each assay. This variability is shown in data from external quality assessment distributions. As a result, the updated guidance is too generalised for use with all the commercial TG2 kits and is therefore not translatable for use in all centres.

Key Words: coeliac disease, ESPGHAN guidelines, tissue transglutaminase antibodies

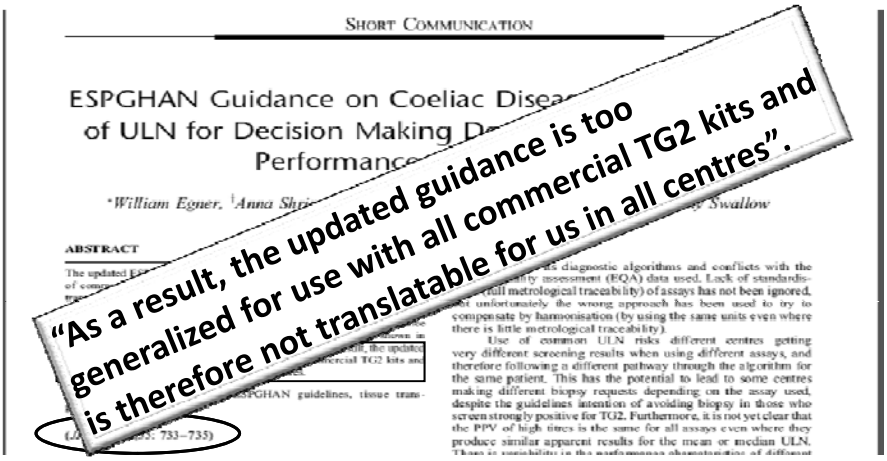
(*JPGN* 2012;55: 733–735)

use of titres in its diagnostic algorithms and conflicts with the external quality assessment (EQA) data used. Lack of standardisation (full metrological traceability) of assays has not been ignored, but unfortunately the wrong approach has been used to try to compensate by harmonisation (by using the same units even where there is little metrological traceability).

Use of common ULN risks different centres getting very different screening results when using different assays, and therefore following a different pathway through the algorithm for the same patient. This has the potential to lead to some centres making different biopsy requests depending on the assay used, despite the guidelines intention of avoiding biopsy in those who screen strongly positive for TG2. Furthermore, it is not yet clear that the PPV of high titres is the same for all assays even where they produce similar apparent results for the mean or median ULN.

Celiac Disease

Confirming the Dx


SHORT COMMUNICATION

ESPGHAN Guidance on Coeliac Disea
of ULN for Decision Making D
Performanc

William Egner, [1]Anna Shi *Swallow*

ABSTRACT

The updated E
of comm

ESPGHAN guidelines, tissue trans-

(J 2005; 733–735)

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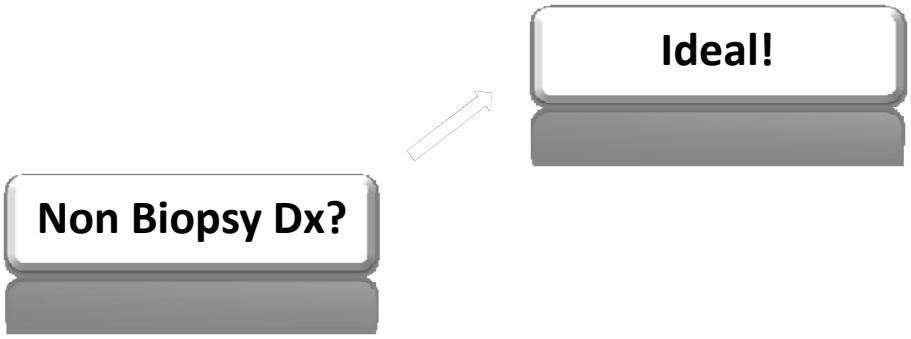
"As a result, the updated guidance is too generalized for use with all commercial TG2 kits and is therefore not translatable for us in all centres".

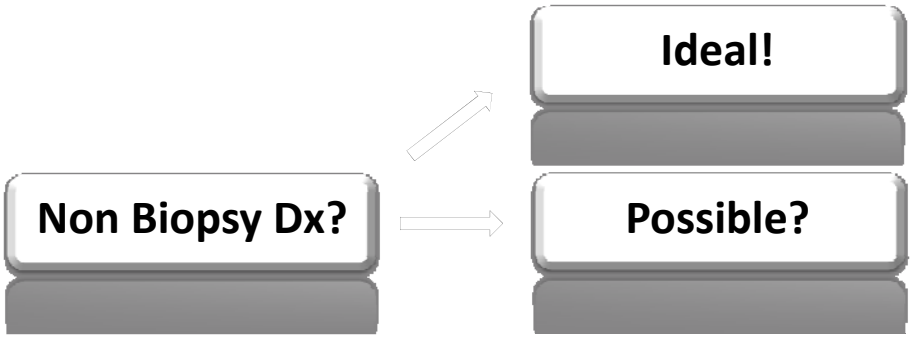
Celiac Disease

Non Biopsy Dx?

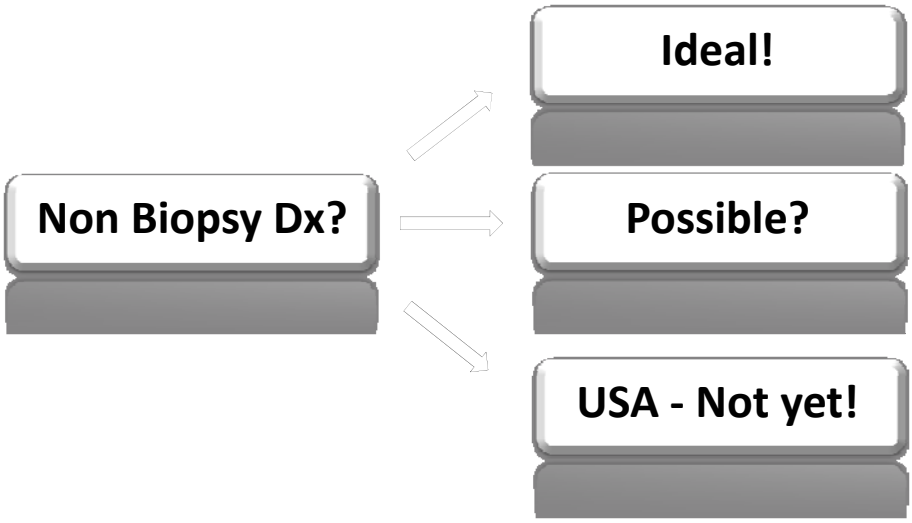
Celiac Disease



Celiac Disease



Celiac Disease



Celiac Disease

Treatment for celiac disease

- **Recommendations**
- **Always confirm before treating**
- **Confirmation mandates GFD for life**
  - **Following a strict GFD is not easy**
  - **Diet has potential QOL implications**
- **Failure to treat has potential long term adverse health consequences**
  - **increased morbidity and mortality**

Celiac Disease

- Celiac disease- current treatment

  - Strict GFD for Life!
  - Skilled nutritionist
    - assessment and education
  - Follow-up
    - growth/health monitoring
    - serological resolution

Celiac Disease

- Celiac disease –future treatment?

Alternatives to the GFD?

- digestive enzymes
- biologics

Prevention?

- infant feeding practices
- vaccines

Celiac Disease

- Resources
- www.gikids.org (click on celiac disease)
- Guidelines for evaluation and management
  - Patient information brochures
  - Start up diet
  - Gluten free drug list
- NASPGHAN guidelines – JPGN 2005;40:1-19.
- NIH Consensus Conference – Gastroenterology 2005:S1-S9.
- AGA guidelines – Gastroenterology 2006;131:1977-1980.
- Technical Review – Gastroenterology 2006;131:1981-2002.
- ESPGHAN guidelines – JPGN 2012;54:136-160.

Presentation of Celiac Disease in Adults

Sheryl Pfeil, MD
Associate Professor – Clinical
Department of Internal Medicine
Division of Gastroenterology, Hepatology & Nutrition
The Ohio State University Wexner Medical Center

Presentation of Celiac Disease in Adults

- Delay in diagnosis common ("celiac iceberg")
- May be diagnosed at any age
- No weight exclusion
- Geographically widespread

Presentation of Celiac Disease in Adults

- Frequent cause of unexplained iron deficiency
- GI symptoms: diarrhea, bloating, "IBS" type symptoms
- Spectrum of severity and symptoms; majority have mild symptoms; mono- or oligosymptomatic
- Non-GI manifestations and celiac associated conditions

Celiac Disease and Iron Deficiency in Adults

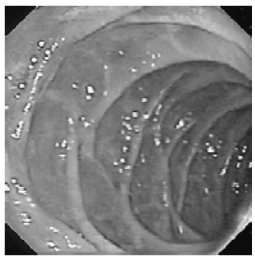
- 5-8% of adults with unexplained iron deficiency anemia have CD
- Many patients undergoing EGD for anemia do not get duodenal biopsies
- Macroscopic and microscopic findings
- Biopsy duodenal bulb and descending duodenum

(2 + 4)

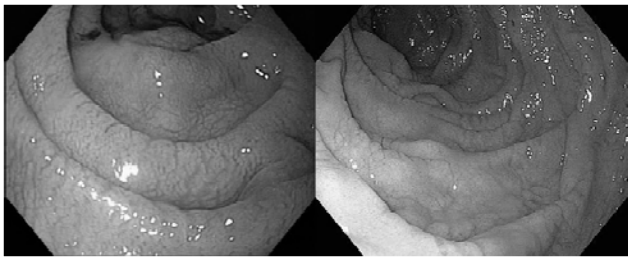
Endoscopic "Clues" in Diagnosis of Celiac Disease

- Loss of duodenal folds
- Fissuring or scalloping along folds
- Nodularity
- Mosaic pattern

Endoscopic "Clues" in Diagnosis of Celiac Disease

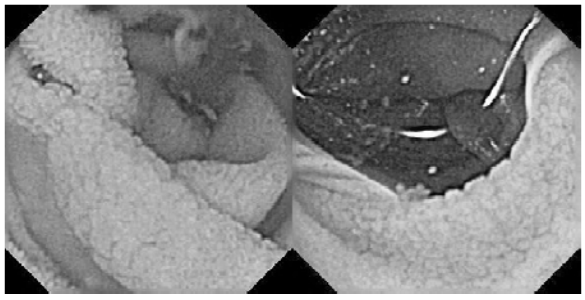


Normal Duodenum



Celiac Disease

Endoscopic "Clues" in Diagnosis of Celiac Disease



Capsule Endoscopy in Celiac Disease

Microscopic Diagnosis of Celiac Disease

- Spectrum of change
- "False positive" biopsies (NSAIDs, olmesartan, tropical sprue, autoimmune enteropathy, self-limited enteritis, Crohn's)
- Correlate with serologies and HLA type

Abnormal Liver Tests and Celiac Disease

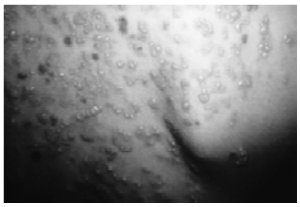
- Incidental elevated transaminases (ALT, AST): up to 9% may have “silent” celiac disease
- Non-specific reactive hepatitis
- Liver tests normalize on a gluten free diet
- Other associated autoimmune liver disorders
  - Primary biliary cirrhosis
  - Autoimmune hepatitis

Conditions Associated with Celiac Disease in Adults

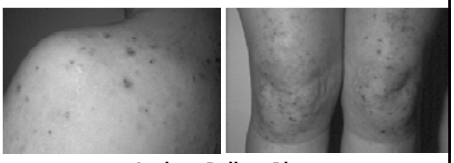
- Dermatitis herpetiformis
- Cerebellar ataxia
- Arthralgias
- Osteoporosis
- Reproductive disorders
- Small bowel malignancies (lymphoma and adenocarcinoma)

Dermatitis Herpetiformis

- Symmetric pruritic papules and vesicles on forearms, knees, buttocks
- Majority (90%) no GI symptoms
- Majority (75+% have increased IEL's or villous atrophy)
- Gluten sensitive
- Responds to gluten withdrawal



CDC



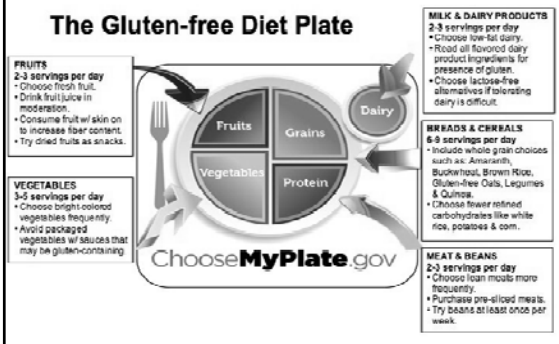
Author: BallenaBlanca

Osteopenia and Osteoporosis

- Early fractures often without GI symptoms
- Secondary hyperparathyroidism due to vitamin D deficiency
- Peripheral > axial bone loss
- Partial reversal on gluten free diet
- Perform DXA scan at diagnosis

Treatment of Celiac Disease

Author: Gérard Lorenz



- Gluten free diet
- Dietician referral
- Motivation: reduced complications
- Explosion of gluten free food industry

Author: DryPot

Early Management of the Adult Celiac Patient

- Confirm diagnosis before treatment
- Diet instruction and support
  - Gluten free diet for life
  - Avoid wheat, barley, and rye
- Test for (and correct) nutrient deficiencies
- DXA scan to evaluate for bone loss

Early Management of the Adult Celiac Patient

- Follow response to therapy
- Recheck serology (if initially positive)
- Support group

Late Management of the Adult Celiac Patient

- **Annual visit**
- **Repeat DXA scan (and vitamin D testing) depending on initial results**
- **May check serology (if initially positive) and routine labs (CBC, metabolic panel)**
- **Symptom flare: think inadvertent gluten ingestion, microscopic colitis, less likely malignancy**

Celiac Disease Dilemmas

- **Self-imposed gluten free diet - confounds diagnostic testing (except HLA type)**
- **The patient who will not eat gluten**
  - **OK if nutritionally sound**
- **"Diagnosis" on basis of single positive test (e.g. gliadin antibodies, HLA type)**
- **Gluten "sensitivity"**

Summary Points

- **Test before treating**
- **You won't find what you don't look for: associated conditions and endoscopic findings**
- **Use the best serology strategy (Ig A anti-tTG Ab) if not Ig A deficient**

Summary Points

- **Recognize risk groups and remember iron deficient anemia**
- **Diet "cures" the manifestations of the disease**
- **Follow the patient**