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

Diagnosed
Undiagnosed

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

Who to test?

- Symptomatic
  - “typical” – first line test
  - “less typical” - consider

How to test?

How to Treat?
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 sx's more common later.

Celiac Disease

• Symptomatic group
  – Gastrointestinal – early onset
  – Age – 6 mths – 2 yrs

Abdominal distention
Anorexia
Weight loss
Wasting
Diarrhea
Steatorrhea
Celiac Disease

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

  - Transaminitis
  - Anorexia
  - Weight Loss
  - Nausea
  - Vomiting
  - Diarrhea
  - Steatorrhea
  - Pain
  - Bloating
  - Flatulence

Symptomatic group
Non-Gastrointestinal

Skin and mucous membranes
- Dermatitis herpetiformis
- Aphthous ulcers

Musculoskeletal system
- Short stature
- Rickets
- Osteopenia
- Osteoporosis
- Arthritis
- Fractures

Hematological system
- Anemia
  - iron deficiency
  - folate/B12
- Leukopenia
- Bruising/bleeding
  - vitamin K deficiency
  - platelet dysfunction
Celiac Disease
Symptomatic group
Non-Gastrointestinal

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

- Dental enamel hypoplasia

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

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

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

Yes

Not so fast!!
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
Testing the Asymptomatic Debate

Guidelines

Who to test?
How to treat?
Celiac Disease

Commerically available tests

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

Recommended Testing for Celiac Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (percent)*</th>
<th>Specificity (percent)*</th>
<th>Technology</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA AGA</td>
<td>80 (52-100)</td>
<td>85 (47-100)</td>
<td>Low</td>
<td>$</td>
</tr>
<tr>
<td>IgG AGA</td>
<td>80 (42-100)</td>
<td>80 (47-94)</td>
<td>Low</td>
<td>$</td>
</tr>
<tr>
<td>IgA tTG</td>
<td>95 (86-100)</td>
<td>96 (90-98)</td>
<td>Low</td>
<td>$$*</td>
</tr>
<tr>
<td>IgA EMA</td>
<td>90 (86-100)</td>
<td>98 (94-100)</td>
<td>High</td>
<td>$$$$</td>
</tr>
<tr>
<td>IgA DGP</td>
<td>88 (74-100)</td>
<td>90 (80-95)</td>
<td>Low</td>
<td>$$*</td>
</tr>
<tr>
<td>IgG DGP</td>
<td>80 (70-95)</td>
<td>98 (90-100)</td>
<td>Low</td>
<td>$$*</td>
</tr>
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*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

Genetic tests for celiac disease

- HLA - DQ2/8
Celiac Disease

Genetic tests for celiac disease

- HLA - DQ2/8
- Non-HLA (39)

Celiac Disease

Genetic tests for celiac disease

- HLA - DQ2/8
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HLA genes in celiac disease

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

The Gene Dose Effect*

<table>
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<tr>
<th>Relative risk</th>
<th>DQA1*0501</th>
<th>DQB1*0201</th>
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<tr>
<td>DQ2 homozygous</td>
<td>DQA1*0501</td>
<td>DQB1*0201</td>
</tr>
<tr>
<td>DQ2 + DQB1*02</td>
<td>DQA1*0501</td>
<td>DQB1*0201</td>
</tr>
<tr>
<td>DQ2 + DQ/X</td>
<td>DQA1*0501</td>
<td>DQB1*0201</td>
</tr>
</tbody>
</table>

- Increased peptide binding & gluten specific T cell response #

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

How to use HLA - DQ2/8

- Specific alleles
- Not for diagnosis
- Selective use

Definitive Testing

Is a biopsy needed in all cases?

- Yes
- Yes
- Yes
- No
Celiac Disease

Confirming the Dx

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

Celiac Disease

Non Biopsy diagnosis?

Symptomatic + tTG >10x ULN

Celiac Disease

Non Biopsy diagnosis?

Symptomatic + tTG >10x ULN

EMA +ve
HLA DQ 2/8
Non Biopsy diagnosis?

Symptomatic + tTG >10x ULN

EMA +ve HLA DQ 2/8

Symptoms resolve Serology resolves

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.

Confirming the Dx

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

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

Confirming the Dx

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

Wiliam Aigner, Thomas Hopfmeister, Sebastian Henricks, Ulrich Fried, and Markus Donohue

The recent ESPCHAN guidelines on celiac disease recommend using a multiple of the upper limit of normal (ULN) to decide whether a patient is celiac disease positive. Some laboratories use varying multiples (3x, 5x, 10x, etc.) and discordance is common. The aim of this study was to evaluate the performance of different threshold multiples. The authors used ROC curve analysis to determine the best threshold. They concluded that using multiples of 3x ULN or higher had the highest sensitivity and specificity.

Conclusions:
1. A threshold of 3x ULN was found to be the best discriminator between celiac disease and non-celiac disease. This threshold had the highest sensitivity and specificity.
2. Alternative thresholds, such as 5x or 10x ULN, may be used, but they will result in lower sensitivity and specificity.
3. The use of a single threshold multiple of ULN is not harmonised across laboratories.

As a result, the updated guidance is too generalised for use with all commercial TG2 kits and is therefore not translatable for use in all centres.
Non Biopsy Dx? Possible?

USA - Not yet!

• 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 - 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

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 |

### 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) |

### 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 |

### 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

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

### 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

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

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### 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

<table>
<thead>
<tr>
<th>Test before treating</th>
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<tr>
<td>You won't find what you don't look for: associated conditions and endoscopic findings</td>
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<tr>
<td>Use the best serology strategy (Ig A anti-tTG Ab) if not Ig A deficient</td>
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### Summary Points

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<th>Recognize risk groups and remember iron deficient anemia</th>
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<td>Diet &quot;cures&quot; the manifestations of the disease</td>
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<tr>
<td>Follow the patient</td>
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