Follow-up of Celiac Disease

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Disclosures

• None
Follow-up

- Feels well
- Feels unwell
Follow-up

- Feels well
- Feels unwell
How Am I Doing?
Gluten-Free Diet
Optimising delivery of care in coeliac disease – comparison of the benefits of repeat biopsy and serological follow-up

L. M. Sharkey*, G. Corbett*, E. Currie†, J. Lee†, N. Sweeney† & J. M. Woodward*
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Diagram:

Persisting villous atrophy

Further (Third) biopsy
N = 94

No gluten contamination
SSD
N = 29

Normal mucosa
N = 7

Minor changes
N = 11

Ongoing VA
N = 11

Gluten contamination
dietary advice
N = 65

Normal mucosa
N = 14

Minor changes
N = 15

Ongoing VA
N = 36
Optimising delivery of care in coeliac disease – comparison of the benefits of repeat biopsy and serological follow-up

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Conclusions
Serology appears to be a poor surrogate marker for mucosal recovery on a gluten-free diet; dietary assessment fails to identify a potential gluten source in many patients with ongoing villous atrophy. The benefits of re-biopsy on diet include stratification of patients with coeliac disease suitable for early discharge from secondary care or those requiring more intensive clinical management.
Does Follow-Up Histology Matter?

- Patients with biopsy-confirmed celiac disease identified through biopsy reports from all (n=28) Swedish pathology departments
- Biopsy data matched by PIN to Total Population Register and Swedish Cause of Death Register

Patients

• Inclusion: Histologic evidence of CD, with follow-up biopsy between 6 months and 5 years after initial diagnosis
• Exposure: Persistent villous atrophy (Marsh 3)
• Outcomes: Mortality, lymphoma, fracture, cardiac outcomes, obstetric outcomes
• Covariates:
  • Age, gender, calendar period, duration of disease, educational attainment
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1.01 (0.86-1.19)</td>
<td>No increased risk</td>
</tr>
<tr>
<td>(Aliment Pharmacol Ther 2013;37:332-9.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>0.97 (0.73-1.30)</td>
<td>No increased risk</td>
</tr>
<tr>
<td>(PLOS One 2015; 30;10:e0117529.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>0.98 (0.41-2.39)</td>
<td>No increased risk</td>
</tr>
<tr>
<td>(Clin Gastroenterol Hepatol 2015;13:1111-7.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoproliferative Malignancy</td>
<td>2.26 (1.18-4.34)</td>
<td>Increased risk</td>
</tr>
<tr>
<td>(Ann Intern Med 2013;159:169-75.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>1.67 (1.05-2.66)</td>
<td>Increased risk</td>
</tr>
<tr>
<td>(J Clin Endocrinol Metab 2014;99:609-16.)</td>
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</tbody>
</table>
What to Tell Patients?

• The risk of lymphoma, while increased, remains low.

• Among 1000 patients with celiac disease followed for 10 years...
  – 7 out of 1000 will develop lymphoma
  – Persistent villous atrophy: 10 out of 1000
  – Healing: 4 out of 1000
How Strong is the Case for Follow-Up Biopsy?

• Observational data
• Risk stratification → small absolute risks
• Guidelines not firm
• Can be offered, but reasonable to defer if:
  – Completely asymptomatic
  – Negative serologies
  – Reassuring dietitian assessment
Examples

• 29 y/o F diagnosed 3 years ago, was minimally symptomatic; TTG normalized, rare symptoms when eating out. Doesn’t ask too many questions at restaurants.

• 36 y/o M diagnosed 2 years ago; TTG remains 1-2 points above normal. Feels well but is distressed about the failure to “normalize.” Is very strict but eats gluten-free oats.

• 40 y/o F with longstanding IBS, then found to have celiac disease 3 years ago. Serologies normalized, IBS symptoms (gas/bloat/urgency) unchanged.
What Happens in the Real World?

Gary Falk
@DrGaryFalk

Are routine biopsies for #celiac disease the right road to take in follow-up treatment? Share your view on the new #agaperspectives debate

1:15 PM - 30 Nov 2016

52% Yes

48% No
# Follow-Up Histology in Children: USA

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of subjects</th>
<th>Persistent villous atrophy</th>
<th>TTG+ among those with villous atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston</td>
<td>103</td>
<td>19%</td>
<td>43%</td>
</tr>
<tr>
<td>New York</td>
<td>53</td>
<td>40%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Borlack, et al. DDW 2017; Sa1296.
Follow-Up Histology According to Age: Sweden

![Graph showing persistent villous atrophy (%) across different age groups and time periods.]

## Medical Follow Up

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Frequency</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietitian</td>
<td>At least once</td>
<td>Gluten avoidance Calories Vitamins Fiber</td>
</tr>
<tr>
<td>Check symptoms</td>
<td>3-4 times during first year Annually</td>
<td></td>
</tr>
<tr>
<td>TTG, confirm adherence</td>
<td>3-4 times during first year Annually</td>
<td>Should normalize in 6-12 months</td>
</tr>
<tr>
<td>Nutritional status</td>
<td>At diagnosis Annually</td>
<td>CBC, iron studies, B12 folate, (25)-D</td>
</tr>
<tr>
<td>Bone density</td>
<td>At diagnosis</td>
<td>(Adults)</td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td></td>
<td>Slightly increased risk of PNA</td>
</tr>
<tr>
<td>Follow-up biopsy</td>
<td>2 years after diagnosis</td>
<td>Controversial</td>
</tr>
</tbody>
</table>
Follow Up: Additional Circumstances

• Contemplating pregnancy
  – Data reassuring after diagnosis of celiac disease
  – Mucosal healing does not affect neonatal outcomes

• Screening family members
  – USPSTF: insufficient evidence *if asymptomatic*
  – “Insufficient” to recommend *for or against* screening

• Transition from childhood to adulthood
  – Medical self-management
  – Education
  – Transition guidelines (Ludvigsson, et al Gut 2016)
More Tools To Monitor

• Gluten peptide detection
  – Stool
  – Urine

• Gluten detection devices

• Clinical prediction scores
  – Symptoms
  – Adherence
  – Quality of Life

• Incorporation into management?
Follow-up

- Feels well
- Feels unwell
Non-Responsive Celiac Disease

• Common:
  – Not celiac disease
  – Inadvertent gluten exposure
  – Bacterial overgrowth of the small intestine
  – Irritable Bowel Syndrome
  – Lactose intolerance
  – Pancreatic exocrine insufficiency
  – Microscopic colitis

• Uncommon: Refractory Celiac Disease type 1

• Rare: Refractory Celiac Disease type 2
What About Relying on Symptoms?

- Subjects with celiac disease of ≥1 year duration and persistent symptoms (n=1345).
- Pre-biopsy interview querying:
  - Bloating
  - Abdominal pain
  - Tiredness
  - Diarrhea
  - Nausea
  - Constipation
  - Depression/anxiety
  - Heartburn
  - Headache
  - Anemia

What About Relying on Symptoms?

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Proportion with villus atrophy (VH:CD ≤2)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Bloating</td>
<td>431/1167 (36.9)</td>
<td>80/178 (44.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>410/1134 (36.2)</td>
<td>101/211 (47.9)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>421/1129 (37.3)</td>
<td>90/216 (41.7)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>275/1018 (36.8)</td>
<td>126/227 (41.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>239/690 (34.6)</td>
<td>272/655 (41.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>263/684 (38.5)</td>
<td>248/661 (37.5)</td>
</tr>
<tr>
<td>Depression/anxiety</td>
<td>173/431 (40.1)</td>
<td>338/914 (37.0)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>140/326 (42.8)</td>
<td>371/1018 (36.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>112/320 (35.0)</td>
<td>399/1025 (38.9)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>114/262 (43.5)</td>
<td>397/1083 (36.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80/179 (44.7)</td>
<td>431/1166 (37.0)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>31/89 (34.8)</td>
<td>480/1256 (38.2)</td>
</tr>
</tbody>
</table>

What About Relying on Symptoms?

### Table 5 | Multiple logistic regression of factors associated with persistent villus atrophy (VH:CD ≤2)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td>0.80</td>
<td>0.54–1.19</td>
<td>0.268</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.83</td>
<td>0.57–1.19</td>
<td>0.311</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.79</td>
<td>0.60–1.03</td>
<td>0.083</td>
</tr>
<tr>
<td>Heartburn</td>
<td>0.89</td>
<td>0.62–1.26</td>
<td>0.497</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1.22</td>
<td>0.88–1.68</td>
<td>0.236</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.81</td>
<td>0.54–1.20</td>
<td>0.300</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
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</table>

Benefits of a Follow-up Biopsy

Symptomatic Patients
• Diagnose/rule out refractory CD
• Identify whether gluten exposure contributes to symptoms
• Identify alternative causes of symptoms

Asymptomatic Patients
• Assess dietary adherence
• Risk-stratify patients for intensive dietician f/u
• Risk-stratify patients for complications

AGA Perspectives December 2016
Getting from NRCD to RCD

Conclusions

- Follow-up biopsy provides information that complements clinical, serological, and dietitian assessment
- Can be incorporated into clinical management pathways
- Non-responsive celiac disease has multiple etiologies
  - RCD is rare but important
• Community of investigators, health professionals
• Career development award sponsored by Celiac Disease Foundation
• Sign up at NASSCD.org
International Celiac Disease Symposium 2017

17th International Celiac Disease Symposium
September 8th - 10th, 2017 | Le-Meridien, New Delhi, India