To biopsy or not to biopsy: that is the question!
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And if yes, when?
- At diagnosis
- At follow-up
Biopsy-avoiding diagnostic pathway for coeliac disease

European Society for the Study of Paediatric Gastroenterology, Hepatology and Nutrition criteria

Reilly et al. 2018
Adults at diagnosis

- **Guidelines:** Adults always undergo biopsy

- **It that always necessary?**

**A subgroup of adults** with CeD might not need a biopsy, previous evidences:

- Tortora et Al, APT 2014
- Fuchs V et Al, l APT  Feb 2019
- Marks L et Al, UEGW 2018
Main issues *pro* biopsy

- **Endoscopy is a safe** procedure
- **We may miss another diagnosis**
- **Precision in diagnosis** - some diagnoses with low titre/contrasting abs anti-TG2 level could represent a false positive
- **Potentials** would go right away on GFD
- **We may miss complications**: Avoiding biopsy is claimed to delay the diagnosis of RCD:
  - 30% persistent symptoms following GFD, then endoscopy to rule out complications, overlapping diseases, and RCD
• ESPGHAN criteria in adults, a prospective analysis

• 443 pts 2008-2016 GI symptoms 60-70% TTG IgA 10x

• TTG +EMA predicting VA in 98,6%

IgA tTG level 10x the ULN had a PPV of 100% for VA
Risk of complications in coeliac patients depends on age at diagnosis and type of clinical presentation  

Biagi et al  DLD 2018

• 1999 -- 2015, 2225 adult CeD patients

• 17 of them developed a complication and 29 died

>60 years at diagnosis the risk increased of 18x vs 18–40 ys and 9x than vs 40–60 years

Classical presentation increases the risk of complications 7x compared to non-classical presentation

In asymptomatic patients the risk of complication is virtually absent
Main issues *contra* biopsy

- **Serology has a high ppv** (no other test has such a ppv!)
- Patients with positive TTG may **refuse the** endoscopy
- Endoscopy and histology are expensive and invasive
- In the vast majority of cases, histology confirms the diagnosis of CeD suggested by serology
- Sometimes (or often) the biopsies are few, non-oriented, and pathologists will not appropriately describe the mucosa
Orientation is the key of success

Computerized 3D-model demonstrates the effects of correct and incorrect planes of cutting on readout results.

Specimens: 4 + 2 in bulb

Tavela et al.
Plos One 2013
Tilting the blocks...

Normal mucosa

villous atrophy - crypt hyperplasia

Marsh 0-1

Marsh 3b-3c

From Taavela PONE 2013
Tricks of the trade: How to avoid histological Pitfalls in celiac disease

Alberto Ravelli\textsuperscript{a,*}, Vincenzo Villanacci\textsuperscript{b}

Path res and practice 2011

\textbf{Fig. 4.} Duodenal biopsy not correctly oriented, where it is impossible to define the degree of histological lesion (H&E, 20\texttimes).

\textbf{Fig. 5.} A biopsy that has been cut tangentially due to bad orientation makes it extremely difficult if not impossible to correctly define the villous pattern (H&E).

\textbf{Fig. 6.} (A) The crushing of villi may resemble partial villous atrophy (H&E, 10\texttimes), whereas (B) partial fusion of villi may prevent a correct count of intraepithelial lymphocytes despite CD3 immunostaining (CD3 immunostain, 20\texttimes).
Bulb biopsies

Taavela et al.
Am J Gastro 2015
To biopsy or not to biopsy: we need experts’ opinion and a few studies...
The serological diagnosis of coeliac disease - a step forward

Geoffrey Holmes¹ and Carolina Ciacci²

Future considerations

In recent years there has been a movement away from morphological to serological criteria, to establish the diagnosis of CD and as serological tests are refined and more information accumulates, this is likely to accelerate. A multicentre study using a standardised approach is now required to further explore the serological cut-off that predicts CD in a large number of patients. Such an investigation will also allow the role of endomysial antibodies in a serological diagnosis strategy to be determined. Serological tests for CD are among some of the best performing tests in medicine and gastroenterologists are fortunate to have them available. These have transformed knowledge regarding the prevalence of CD and have aided the diagnosis immeasurably but still have to be used intelligently.
To advance our practice and cement a **no biopsy policy** into adult practice **we require a multi-centre prospective study** which will provide: 1) high quality data on the percentage of adult patients that do not require a biopsy; 2) The PPV and validity of numerous serological titres; 3) The role of HLA in the pathway for adults with suspected coeliac disease. Finally and crucially we require a clear message to all clinicians that positive serology equates to immediate referral to a Gastroenterology Consultant and not a presumptive diagnosis of CD and trial of a GFD in primary care!
Best Practice Advice 2a:

- strongly positive TG2-IgA + EMA in a second blood sample: the ppv for CeD is virtually 100%.

- In adults, esophagogastroduodenoscopy (EGD) and duodenal biopsies may then be performed for purposes of differential diagnosis.
The Bi.A.CeD study

• prospective, multicenter, international study, aimed to evaluate the possibility to avoid duodenal biopsy in a subgroup of patients with suspected CeD

• Collect blood sample and histology of consecutive CeD at diagnosis
• Send the sera to central labs
• Send the histology to central Pathologist
• Follow-up
19 Centres

ITALY
Univ. Salerno, Univ Padua, Univ. Palermo, Univ. Verona, Univ. Pavia, Hospital Santorso. (6 different centers)

7. Hospital de Gastroenterología Dr. C. Bonorino Udaondo Buenos Aires , Argentina
8. Univ. Tampere Finland
9. Dpt of Gastroenterology and Human Nutrition All India institute of Medical Science Ansari Nagar, New Delhi
10. Shahid Beheshti University of Medical Sciences, Tehran-Iran
11. Gastroenterologie si Hepatologie Fundeni – Centru de Excelență acreditat de Ministerul Educației si Cercetării Bucharest, Romania
12. Carol Davila University of Medicine and Pharmacy · Dpt of Internal Medicine and Gastroenterology, Romania
13. University of Oslo · Institute of Clinical Medicine
14. VUmc Amsterdam, Holland
15. Sheffield University UK
16. Servicio de Medicina Interna del Hospital de León, Spain
17. Madrid 1
18. Madrid 2
19. New Zealand
220 patients : symptoms/signs

- Iron deficiency 88/220 40%
- GI symptoms 78/220
- Fatigue 73/220
- Osteoporosis 18/220
- Infertility 10/220
- Asymptomatic 9/220 ~4%
<table>
<thead>
<tr>
<th>serology</th>
<th>Histology, Marsh classification</th>
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<tr>
<td>EMA n 30</td>
<td>Marsh 0* 49</td>
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<tr>
<td>Ttg IgA n 75</td>
<td>Marsh 1* 37</td>
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<td>Ttg + EMA n 115</td>
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220 patients - final diagnosis

2 Autoimmune gastritis
23 IBS
3 Gluten sensitive
4 Gyn anemia
5 Crohn’s
1 Pancreatic cancer
15 I do not know

Celiac disease
133

Other

3 Potentials
Take home message

- in our days, histology is may be the pitfall of CeD diagnosis

- experts and studies suggest that there is the possibility to avoid the biopsy in a subgroup of adults with the suspicion of CeD

- It may be possible that the ESPGHAN criteria may be adopted also in adults (age limitation?)

- A prospective, multicenter, controlled trial is needed (ongoing)
The difficulty lies not so much in developing new ideas as in escaping from old ones

JM Keynes