



ICDS2022SORRENTO

19th INTERNATIONAL CELIAC DISEASE SYMPOSIUM

Toward one protocol for children and adults

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Disclosure of Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

I have served as speaker for EG Stada Group, Fresenius Kabi, Janssen, Pfizer, Takeda, Unifarco, Malesci; has served as consultant for Galapagos

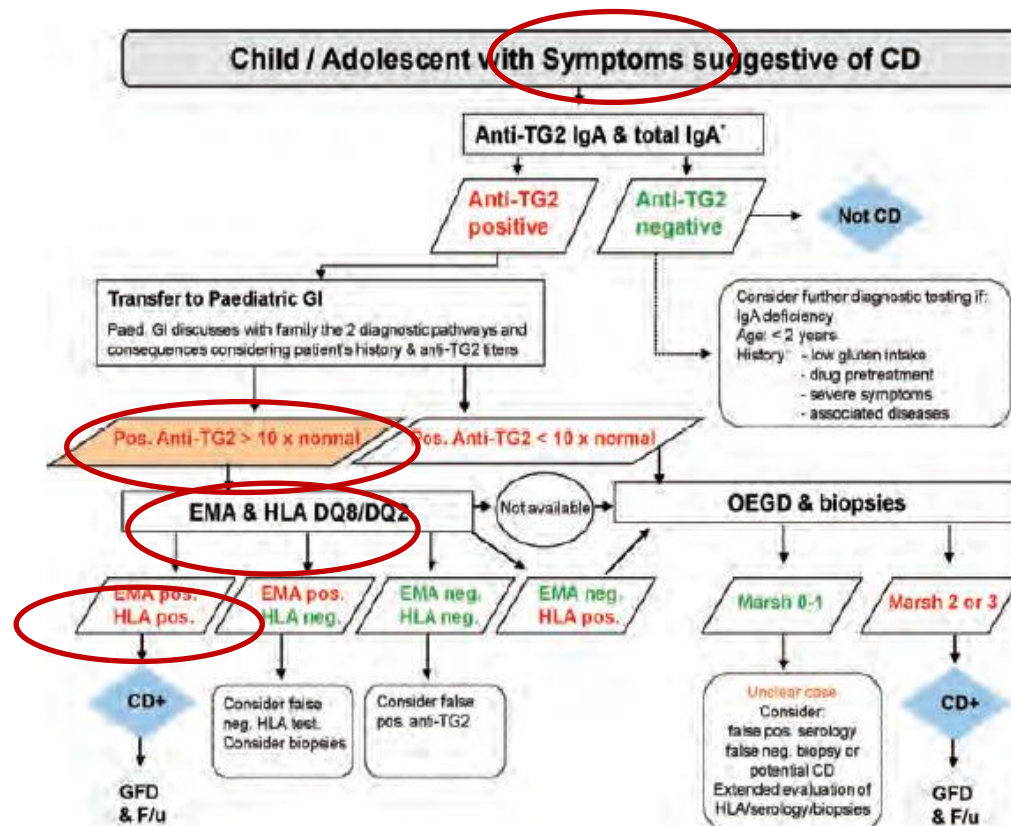


European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease

2012

^{*}S. Husby, [†]S. Koletzko, [‡]I.R. Korponay-Szabó, [§]M.L. Mearin, ^{||}A. Phillips, [¶]R. Shamir,
[#]R. Troncone, ^{**}K. Giersiepen, ^{††}D. Branski, ^{‡‡}C. Catassi, ^{§§}M. Lelgeman, ^{||||}M. Mäki,
^{¶¶}C. Ribes-Koninckx, ^{###}A. Ventura, and ^{****}K.P. Zimmer, for the ESPGHAN Working Group on
Coeliac Disease Diagnosis, on behalf of the ESPGHAN Gastroenterology Committee

JPGN · 2012



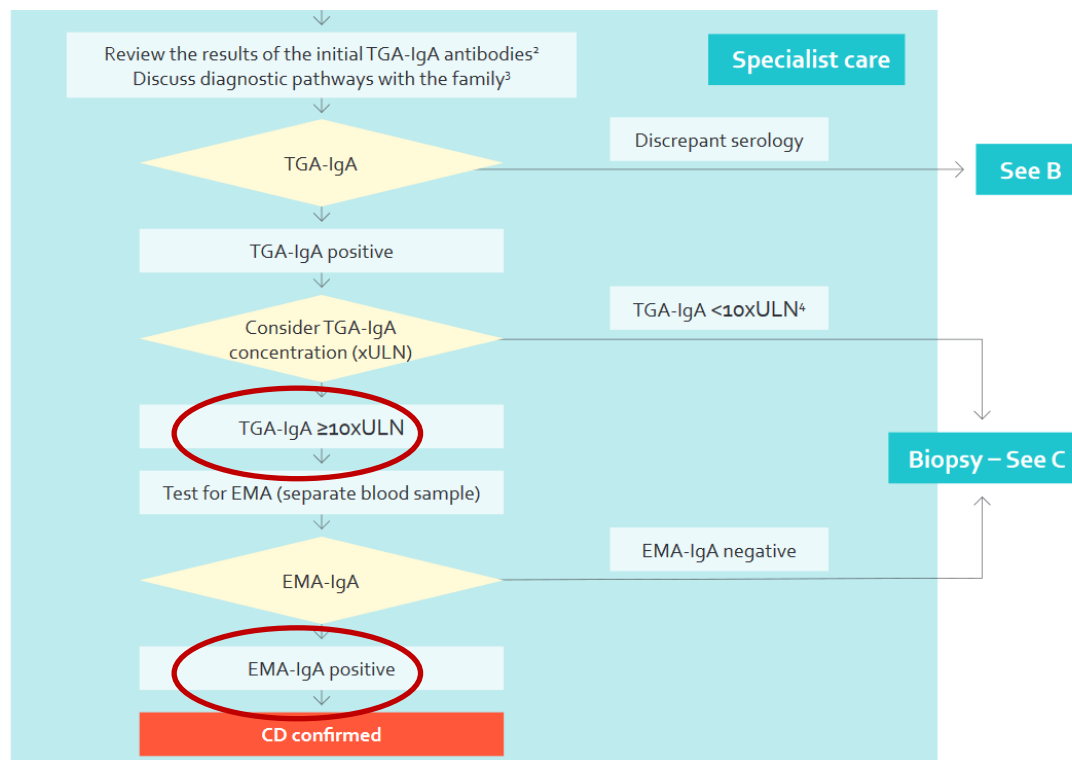


Guidelines for diagnosing coeliac disease: European Society Paediatric Gastroenterology, Hepatology and Nutrition

Sarah Berry ¹, Naomi McMahon,² Jonathan Henderson¹

Arch Dis Child Educ Pract Ed 2021;

2021





Journal of Pediatric Gastroenterology and Nutrition
40:1–19 © January 2005 Lippincott Williams & Wilkins, Philadelphia



Clinical Guideline

Guideline for the Diagnosis and Treatment of Celiac Disease in Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

NASPGHAN Clinical Report on the Diagnosis and Treatment of Gluten-related Disorders

**Ivor D. Hill, †Alessio Fasano, ‡Stefano Guandalini, §Edward Hoffenberg, ||Joseph Levy,
¶Norelle Reilly, and #Ritu Verma*

JPGN • Volume 63, Number 1, July 2016



Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice

Katharina Julia Werkstetter, et al. *Gastroenterology* 2017;

“More than 50% children and adolescents with celiac disease can be diagnosed without biopsies, avoiding the burden of upper endoscopy with anesthesia and saving health care costs”

Validation of Antibody-Based Strategies for Diagnosis of Pediatric Celiac Disease Without Biopsy

Johannes Wolf et al. *Gastroenterology* 2017;

Duodenal biopsies can be avoided in a large proportion of pediatric patients with suspected CD, thereby reducing patient risks, costs, endoscopy waiting times, and delay of treatment.



Are we ready for one protocol for children and adults?

“the gastroenterologists in adult practice have been
reluctant to adopt this approach”



Pros & Cons of a “non biopsy strategy” in Coeliac Disease





Pros: uncomfortable procedure

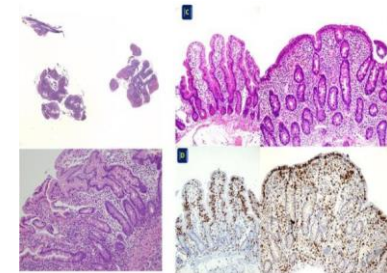
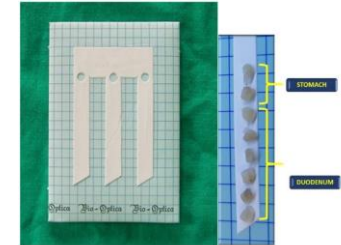
- expensive and invasive
- poorly tolerated by many patients
- risks: sedation - GI bleeding - perforation





Pros: possible misdiagnosis

- Poor quality biopsies
- Inadequate preparation
- Incorrect orientation
- Missing duodenal bulb biopsies
- Histopathologists vary in expertise
- Patchy lesions
- Single-bite technique not used



Collin P et al Eur J Gastroenterol Hepatol 2005
Mubarak A et al. Scand J Gastroenterol 2011
Webb C et al. J Pediatr Gastroenterol Nutr 2011
Arguelles-Grande C et al. J Clin Pathol 2012
Picarelli A et al. Scand J Gastroenterol 2014
Villanacci Transl Med UniSa. 2020



Pros: high accuracy of a 10- fold increase in serum IgA anti-tTg levels for detecting Marsh 3 damage score

1. Sugai E, Moreno ML, Hwang HJ, et al. Celiac disease serology in patients with different pretest probabilities: is biopsy avoidable? *World J Gastroenterol* 2010;16:3144–52.
2. Zanini B, Magni A, Caselani F, et al. High tissue-transglutaminase antibody level predicts small intestinal villous atrophy in adult patients at high risk of celiac disease. *Dig Liver Dis* 2012;44:280–5.
3. Alessio MG, Tonutti E, Brusca I, et al. Correlation between IgA tissue transglutaminase antibody ratio and histological finding in celiac disease. *J Pediatr Gastroenterol Nutr* 2012;55:44–9.
4. Beltran L, Koenig M, Egner W, et al. High-titre circulating tissue transglutaminase-2 antibodies predict small bowel villous atrophy, but decision cut-off limits must be locally validated. *Clin Exp Immunol* 2014;176:190–8.
5. Wakim-Fleming Jamile', Pagadala MR, Lemyre MS, et al. Diagnosis of celiac disease in adults based on serology test results, without small-bowel biopsy. *Clin Gastroenterol Hepatol* 2013;11:511–6.
6. Tortora R, Imperatore N, Capone P, et al. The presence of anti-endomysial antibodies and the level of anti-tissue transglutaminases can be used to diagnose adult coeliac disease without duodenal biopsy. *Aliment Pharmacol Ther* 2014;40:1223–9.
7. Fuchs V, Kurppa K, Huhtala H, Laurila K, Mäki M, Collin P, Salmi T, Luostarinen L, Saavalainen P, Kaukinen K. Serology-based criteria for adult coeliac disease have excellent accuracy across the range of pre-test probabilities. *Aliment Pharmacol Ther*. 2019 Feb;49(3):277–284.
8. Ylönen V, Lindfors K, Repo M, Huhtala H, Fuchs V, Saavalainen P, Musikka A, Laurila K, Kaukinen K, Kurppa K. Non-Biopsy Serology-Based Diagnosis of Celiac Disease in Adults Is Accurate with Different Commercial Kits and Pre-Test Probabilities. *Nutrients*. 2020 Sep 8;12(9):2736
9. Penny HA, Raju SA, Lau MS, Marks LJ, Baggus EM, Bai JC, Bassotti G, Bontkes HJ, Carroccio A, Danciu M, Derakhshan MH, Ensari A, Ganji A, Green PHR, Johnson MW, Ishaq S, Lebowitz B, Levene A, Maxim R, Mohaghegh Shalmani H, Rostami-Nejad M, Rowlands D, Spiridon IA, Srivastava A, Volta U, Villanacci V, Wild G, Cross SS, Rostami K, Sanders DS. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. *Gut*. 2020 Nov 2;gutjnl-2020-320913.



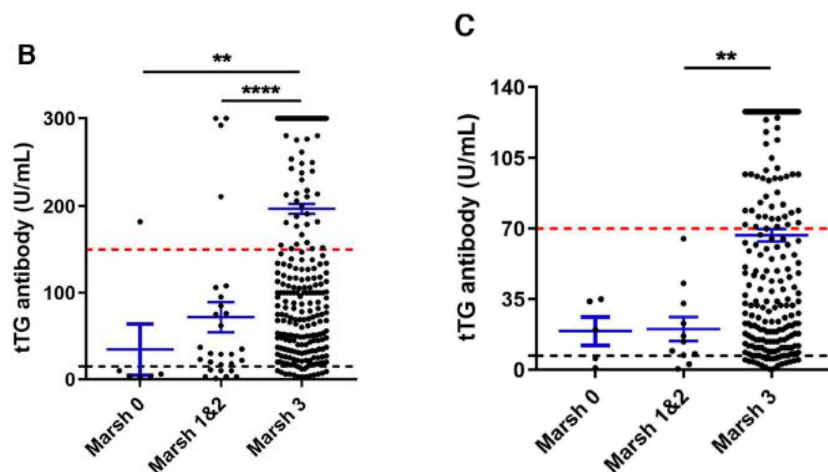
Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts

Hugo A Penny ¹, Suneil A Raju, ¹ Michelle S Lau, ¹ Lauren JS Marks, ¹ Elisabeth MR Baggus, ¹ Julio C Bai, ² Gabrio Bassotti, ³ Hetty J Bontkes, ⁴ Antonio Carroccio, ⁵ Mihai Danciu, ⁶ Mohammad H Derakhshan, ⁷ Arzu Ensari, ⁸ Azita Ganji, ⁹ Peter H R Green, ¹⁰ Matt W Johnson, ¹¹ Saud Ishaq, ¹² Benjamin Lebwohl, ¹⁰ Adam Levene, ¹¹ Roxana Maxim, ¹³ Hamid Mohaghegh Shalmani, ¹⁴ Mohammad Rostami-Nejad, ¹⁴ David Rowlands, ¹⁵ Irene A Spiridon, ⁶ Amitabh Srivastava, ¹⁶ Umberto Volta, ¹⁷ Vincenzo Villanacci, ¹⁸ Graeme Wild, ¹ Simon S Cross, ¹ Kamran Rostami, ¹⁹ David S Sanders ¹

Gut 2021;

Aim: to determine the predictive capacity and diagnostic yield of a 10- fold increase in serum IgA anti-tissue transglutaminase antibody levels for detecting small intestinal injury (Marsh 3)

Cohort 1: 740 patients assessed in the specialist CeD clinic at a UK centre



	≥10x ULN			
	Cohort 1A		Cohort 1B	
	Value	95% CI	Value	95% CI
Sensitivity	59%	55-64%	45%	40-52%
Specificity	85%	69-95%	100%	79-100%
PPV	98.1%	95.8-99.1%	100%	-
NPV	14.2%	12.1-16.5%	10.3%	9.3-11.4%

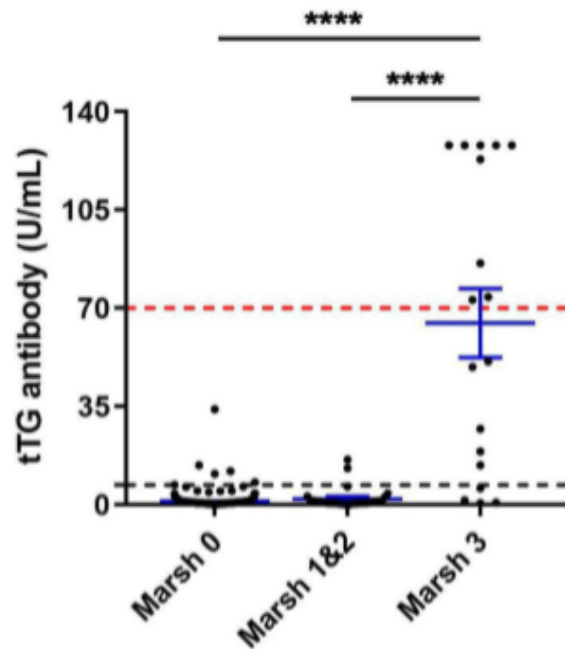


Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts

Hugo A Penny ¹, Suneil A Raju,¹ Michelle S Lau,¹ Lauren JS Marks,¹ Elisabeth MR Baggus,¹ Julio C Bai,² Gabrio Bassotti,³ Hetty J Bontkes,⁴ Antonio Carroccio ⁵, Mihai Danciu,⁶ Mohammad H Derakhshan,⁷ Arzu Ensari,⁸ Azita Ganji,⁹ Peter H R Green,¹⁰ Matt W Johnson,¹¹ Saud Ishaq ¹², Benjamin Lebwohl,¹⁰ Adam Levene,¹¹ Roxana Maxim,¹³ Hamid Mohaghegh Shalmani,¹⁴ Mohammad Rostami-Nejad,¹⁴ David Rowlands,¹⁵ Irene A Spiridon,⁶ Amitabh Srivastava ¹⁶, Umberto Volta,¹⁷ Vincenzo Villanacci,¹⁸ Graeme Wild,¹ Simon S Cross,¹ Kamran Rostami,¹⁹ David S Sanders¹

Gut 2021;

Cohort 2: 532 patients with low suspicion for CeD referred for upper GI endoscopy at a UK centre



	≥10x ULN	
	Value	95% CI
Sensitivity	50%	26-74%
Specificity	100%	99-100%
PPV	100%	-
NPV	98.3%	96.8-99.2%

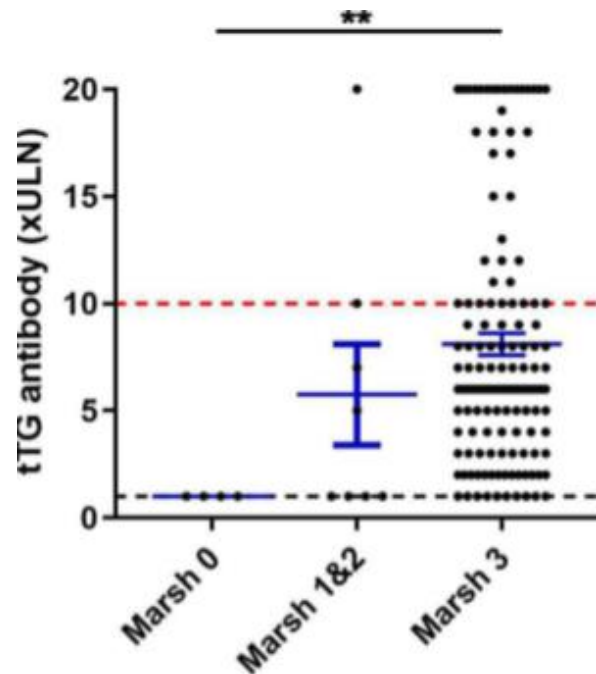


Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts

Hugo A Penny ¹, Suneil A Raju,¹ Michelle S Lau,¹ Lauren JS Marks,¹ Elisabeth MR Baggus,¹ Julio C Bai,² Gabrio Bassotti,³ Hetty J Bontkes,⁴ Antonio Carroccio ⁵, Mihai Danciu,⁶ Mohammad H Derakhshan,⁷ Arzu Ensari,⁸ Azita Ganji,⁹ Peter H R Green,¹⁰ Matt W Johnson,¹¹ Sauid Ishaq ¹², Benjamin Lebwohl,¹⁰ Adam Levene,¹¹ Roxana Maxim,¹³ Hamid Mohaghegh Shalmani,¹⁴ Mohammad Rostami-Nejad,¹⁴ David Rowlands,¹⁵ Irene A Spiridon,⁶ Amitabh Srivastava ¹⁶, Umberto Volta,¹⁷ Vincenzo Villanacci,¹⁸ Graeme Wild,¹ Simon S Cross,¹ Kamran Rostami,¹⁹ David S Sanders¹

¹ Gut 2021;

Cohort 3: 145 patients with raised ab-tTG titres from multiple international sites



	≥10x ULN	
	Value	95% CI
Sensitivity	30%	22-38%
Specificity	83%	52-98%
PPV	95.2%	84.6-98.6%
NPV	9.5%	7.4-12.2%



Pros: this approach is in use



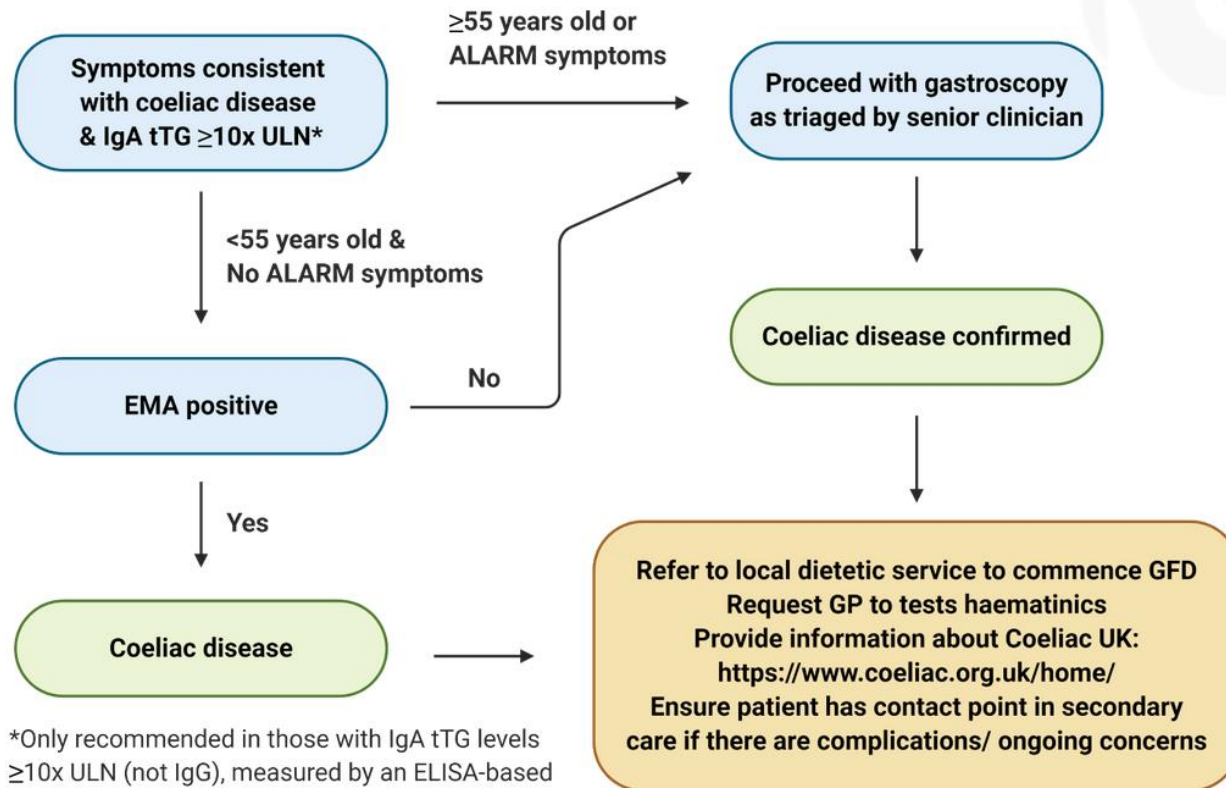
?



COVID-19 Non-biopsy policy for adults with positive coeliac serology

BSG Suggested Protocol Pending Revisions of the BSG Coeliac Disease Guidelines

Penny HA, Sanders DS, Gillett H, Gillett P, Edwards CM.



*Only recommended in those with IgA tTG levels ≥10x ULN (not IgG), measured by an ELISA-based assay.



Coeliac disease

Current Care Summary | Published: 18.12.2018 [Print](#)

Working group appointed by the Finnish Medical Society Duodecim, the Finnish Society of Gastroenterology

Current Care Guideline [1](#) and Summary [2](#) in Finnish

Positive endomysium antibodies (EmA) and high concentrations of tissue transglutaminase antibodies (tTG) have excellent accuracy for coeliac disease. The updated guideline recommends using tTG as the first-line diagnostic investigation. Diagnosis can be made without endoscopy in subjects with tTG >10x upper limit of normal and positive EmA; in other cases intestinal biopsy is needed. Skin biopsy is required for the diagnosis of dermatitis herpetiformis. The treatment is a life-long gluten-free diet initiated under the supervision of a dietitian. The possibility of refractory coeliac disease should be remembered particularly in older persons and in those with inadequate dietary response.

Katri Kaukinen (Chair)

Kalle Kurppa

Ursula Schwab

Kaisa Hervonen

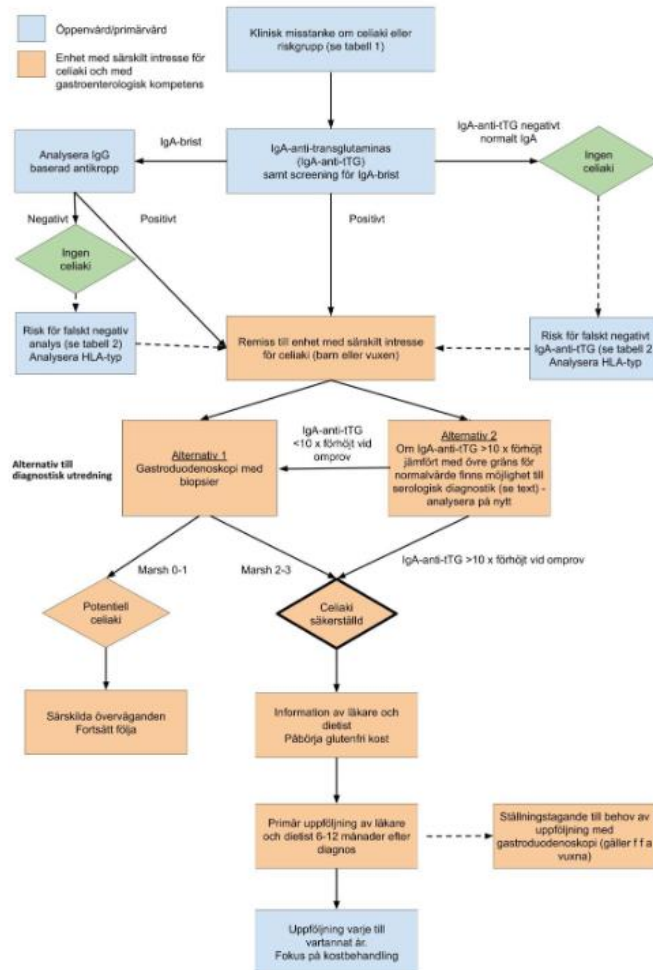
Kaija-Leena Kolho

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Katriina Kukkonen-Harjula

Consultant:

Jorma Komulainen



Diagnos enbart baserad på serologi (IgA-anti-tTG förhöjda >10 gånger övre normalvärdet vid två separata provtillfällen) anses säkert även för vuxna. Övriga ska utredas med gastroduodenoskopi med biopsier från duodenum och bulb för att undvika överdiagnostik

*Diagnosis based solely on serology (IgA-anti-tTG elevated >10 times the upper normal value on two separate test occasions) is **considered safe even for adults**. Others must be investigated with gastroduodenoscopy with biopsies from the duodenum and bulb to avoid overdiagnosis*



Cons: Risk of missing patients with...

- IgA deficiency
- Immunosuppressants
- Seronegative CeD patients



Seronegative coeliac disease: clearing the diagnostic dilemma

3-5%

Annalisa Schiepatti^a, David S. Sanders^b, and Federico Biagi^a 2018

Clinical classification and long-term outcomes of seronegative coeliac disease: a 20-year multicentre follow-up study

Schiepatti A. APT 2021

Conclusions: Seronegative coeliac disease has a more aggressive disease phenotype than seropositive coeliac disease. These data argue against over-reliance on serology for the diagnosis of coeliac disease and support a strict clinical and histologic follow-up in seronegative coeliac disease.



Cons: Risk of missing patients with...

IgA deficiency

Immunosuppressants

Seronegative CeD patients

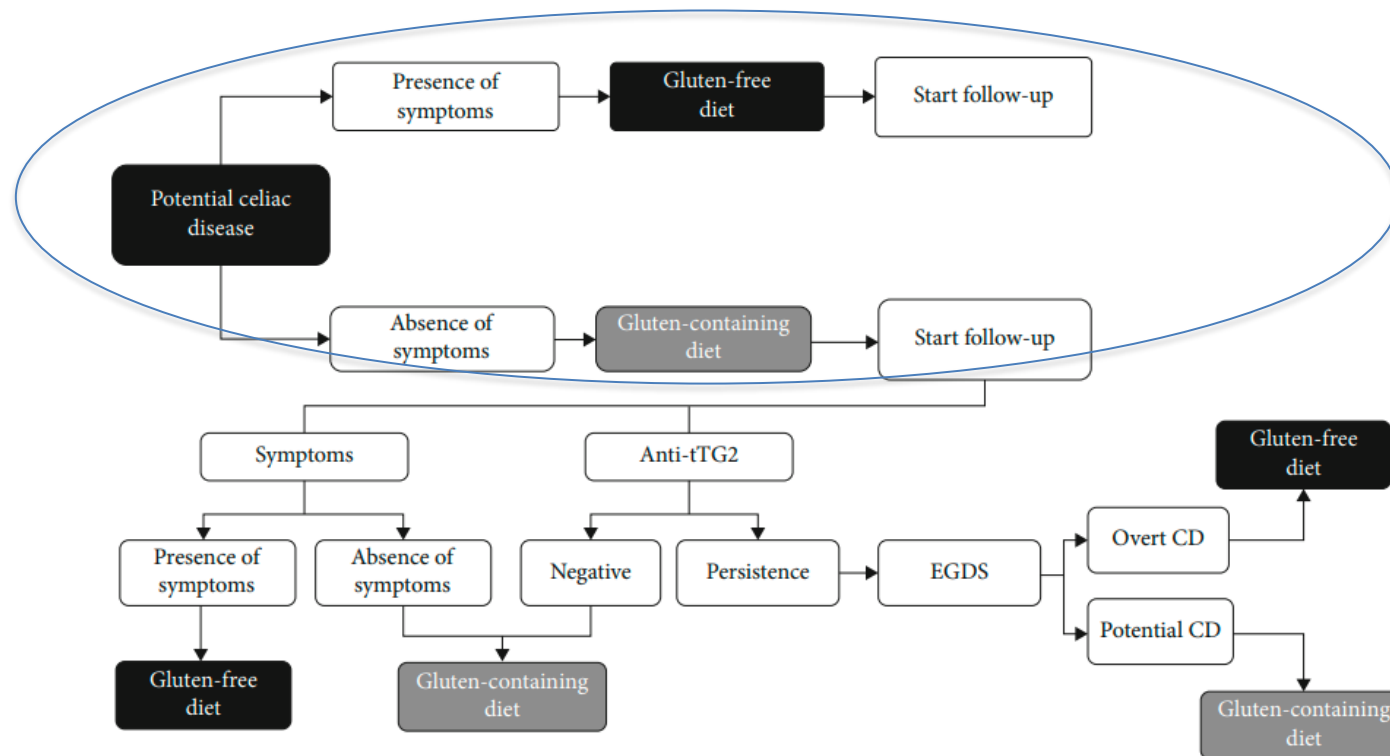
IgA deficiency and people taken immunosuppressants are easily detectable

A non-biopsy approach considers only patients with high serology levels

An OGD should always be performed in cases of high suspicion

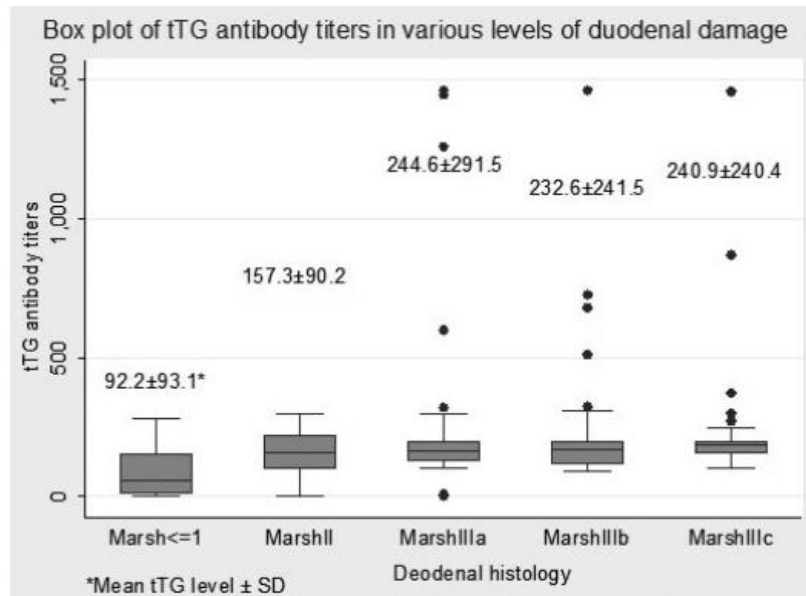


Cons: Risk of an unnecessary GFD in potential CeD

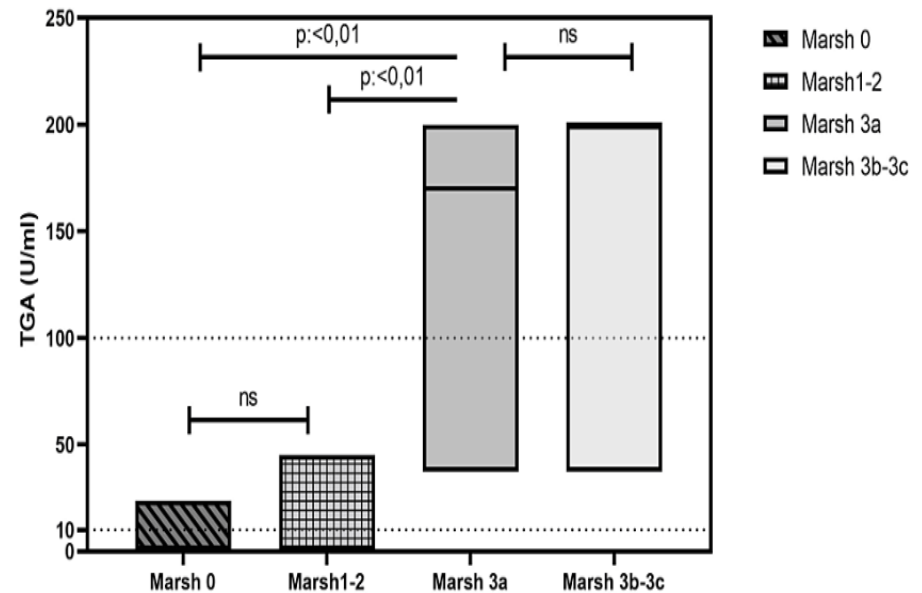




Relationship between the anti-tTG IgA levels and mucosal damage



Rahmati Middle East Journal of Digestive Diseases 2014



Baykan AR Cureus 2022



Cons: Risk of an unnecessary GFD in potential CeD

Symptomatic potential patients generally start a GFD

Positive correlation between serology and duodenal damage



Cons: Risk of missing...

- CeD complications

Risk factors:

- ✓ classical presentation
- ✓ advanced age at diagnosis
- ✓ negative serology
- ✓ homozygosity for HLA-DQ2



Cons: Risk of missing...

- Gastric cancer or other peptic diseases



Low prevalence of upper endoscopic gastrointestinal findings despite high frequency of alarm symptoms at the time of diagnosis in adult coeliac disease

Stiliano Maimaris^a, Annalisa Schieppatti^a, Gian Marco Gabrielli^a, Martina Costetti^a, Stefania Costa^a, David S Sanders^b, Fabiana Zingone^c, Antonio Carroccio^d, Carolina Ciacci^e, Antonio Di Sabatino^f and Federico Biagi^a

European Journal of Gastroenterology & Hepatology 2020

January 1999 to December 2017→

278 patients diagnosed in Pavia
(mean age 35±12years)

- ✓ A gastroscopy was not necessary in 113 (40.6%) patients
- ✓ Major UGI endoscopic findings: 3 cases of autoimmune atrophic gastritis, 19 oesophagitis and 20 Helicobacter pylori infections
- ✓ No organic disorders were found



Upper gastrointestinal endoscopic findings in celiac disease at diagnosis: A multicenter international retrospective study.

Juan P. Stefanolo¹, Fabiana Zingone^{2,3}, Carolina Gizzi⁴, Ilaria Marsilio², María L. Spinetti¹, Edgardo Smecuol¹, Mark Khaouli⁵, María L. Moreno¹, María I. Pinto-Sánchez⁵, Sonia I. Niveloni¹, Elena F. Verdú⁵, Carolina Ciacci⁴, Julio C. Bai^{1,6}.

Two European, one North American centers included biopsy confirmed CeD following positive serology.

One South America center included controls

World Journal of Gastroenterology *in press*

Demographic data and upper GI endoscopic findings	Overall CeD population n (%)	≤ 50 yr n (%)	51-60 yr n (%)	≥61 yr n (%)
N of patients	1328	1140 (85.8)	114 (8.6)	74 (5.6)
Age (median and 25% IQR) yr.	35 (26-43)	33 (25-39)	55 (53-56)	67 (63-71)
Number of females (%)	1064 (80.1)	931 (81.7)	82 (71.9)	51 (41.0)
Patients with positive serology. n (%)	1269 (95.6)	1092 (95.8)	109 (95.6)	68 (91.9)
Patients with at least one significant endoscopic abnormalities. n (%)	135 (10.1)	102 (8.9)*	20 (17.5)	13 (17.6)
Reflux esophagitis with erosions. n (%)	85 (6.4)	69 (6.0)	12 (10.5)	4 (5.4)
Esophageal ulcers. n (%)	1 (0.2)	1 (0.1)	0	0
Esophageal cancer. n (%)	0	0	0	0
Suspicion of metaplasia. n (%)	16 (1.2)	10 (0.9)	3 (2.6)	2 (2.7)
Biopsy confirmed Barrett's esophagus. n (%)	3 (0.2)	2 (0.2)	0	1 (1.3)
Gastric erosions. n (%)	27 (2.0)	20 (1.7)	3 (2.6)	4 (5.4)
Gastric ulcers. n (%)	1 (0.1)	1 (0.1)	0	0
Gastric cancer. n	0	0	0	0
Duodenal erosions. n (%)	15 (1.1)	8 (0.7)	3 (2.6)	4 (5.4)
Duodenal ulcers. n (%)	15 (1.1)	10 (0.9)	4 (3.5)	1 (1.3)
Duodenal cancer. n	0	0	0	0

Although patients over 51 yrs had a high prevalence of non-CeD gastroduodenal mucosal damage, no malignancy or premalignant lesions were found.

Having CeD was associated with a 72% reduction in the risk of any endoscopic abnormality



Cons: Risk of missing...

CeD complications

Other diagnoses

Rare (consider age and other risk factors)

Perform endoscopy in cases of non response



To start thinking of a “Non-biopsy approach”, we need...

- Patient selection
- Standardised criteria



SEROLOGY AS PREDICTOR OF DUODENAL DAMAGE IN ADULTS WITH SUSPECTED CELIAC DISEASE.

The Sorrento position paper derived from a multicenter nested case-control study
Unpublished

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Govind Makharia, **India**
Gingold-Belfer Rachel, **Israel**
Gary Norman, San Diego, **USA**

To evaluate the accuracy of positive serology for CeD diagnosis in a multicenter, prospective study enrolling a large cohort of patients from diverse geographic areas and **to make recommendations for future diagnostic criteria.**



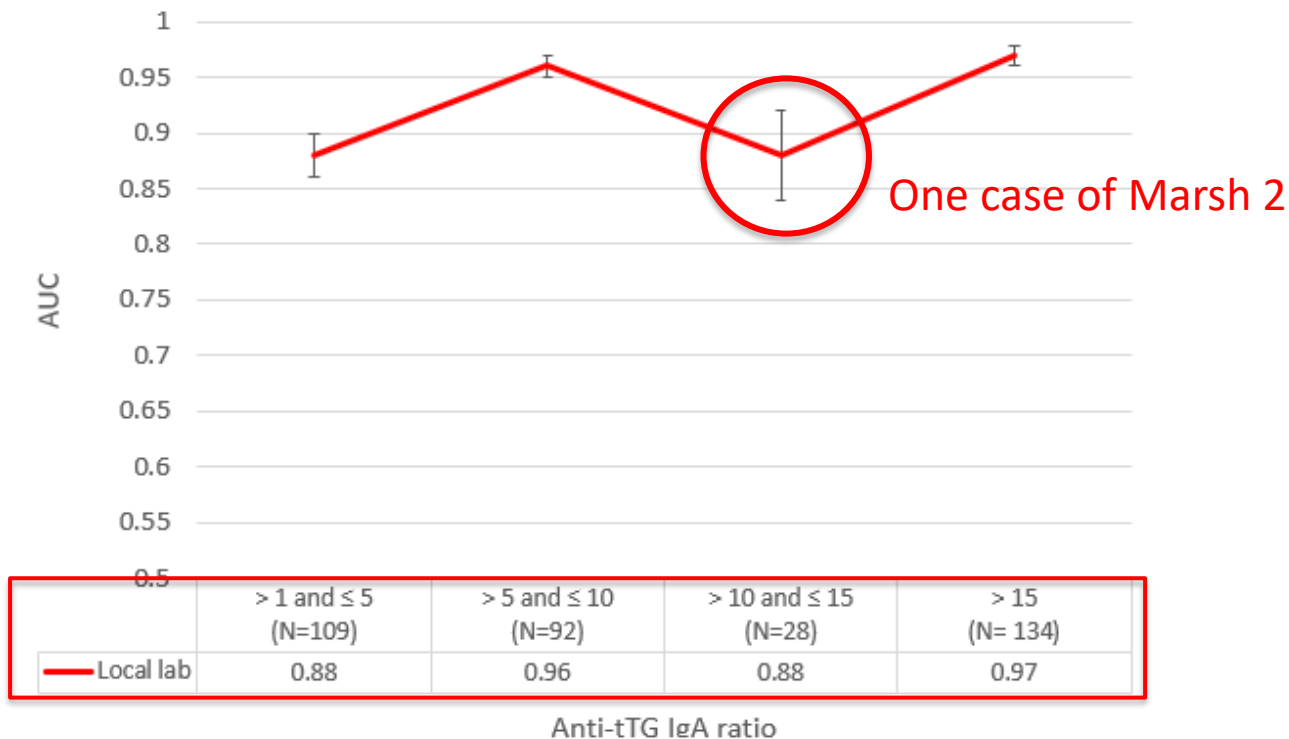
- Study population: all consecutive adult patients seen in the time lapse of 12-24 months with clinical suspicion of CeD or at risk of CeD
- Multicenter, multiethnic study
- Prospective collection of data and serum samples
- Samples were sent to a central laboratory (INOVA, San Diego, US)
- Histological re-evaluation of discordant cases by Dr Villanacci



Main Results

Total population: 436 patients (355 Marsh stage ≥ 3)

The accuracy of positive serology
for CeD diagnosis for detecting Marsh 3 score



Findings were similar in analyses by sex, age, clinical presentation, and presence of associated autoimmune diseases and also using central lab data



Main Results

Using the serology cut-off >X10 ULN, CeD could have been correctly diagnosed without upper endoscopy and histology in 99.4% patients.

- ✓ 34.8 % (8/23) of the discordant cases were due to an incorrect histological evaluation
- ✓ One Barrett oesophagus in a man > 40 years old
- ✓ One T ileum lymphoma post one year from diagnosis



Conclusions

- A serology-based CeD diagnosis without biopsy is possible and safe in adults.
- The authors suggest to adopt the same serology cut-off accepted for the pediatric CeD diagnosis (Anti-tTG IgA X10 ULN) regardless of the kit used.



*We do not want to make the whole world gluten free
But the world simpler... when possible!*

