

اسرھال مزمن سلیاک از تشخیص تا درمان



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CELIAC DISEASE INTRODUCTION

CeD is a Chronic & permanent immune-mediated response to gluten present in wheat, barley, and rye in genetically individuals (HLA-DQ2/DQ8)

A multisystem disorder rather than an isolated intestinal disease

Epidemiology: 1% prevalence 80% undiagnosed

DIAGNOSTIC CRITERIA CELIAC DISEASE

- ◉ Clinical History Wide clinical spectrum
- ◉ multisystem involvement
- ◉ Asymptomatic to symptomatic
- ◉ Serologic testing ((IgA anti-tTG)
- ◉ Duodenal biopsies

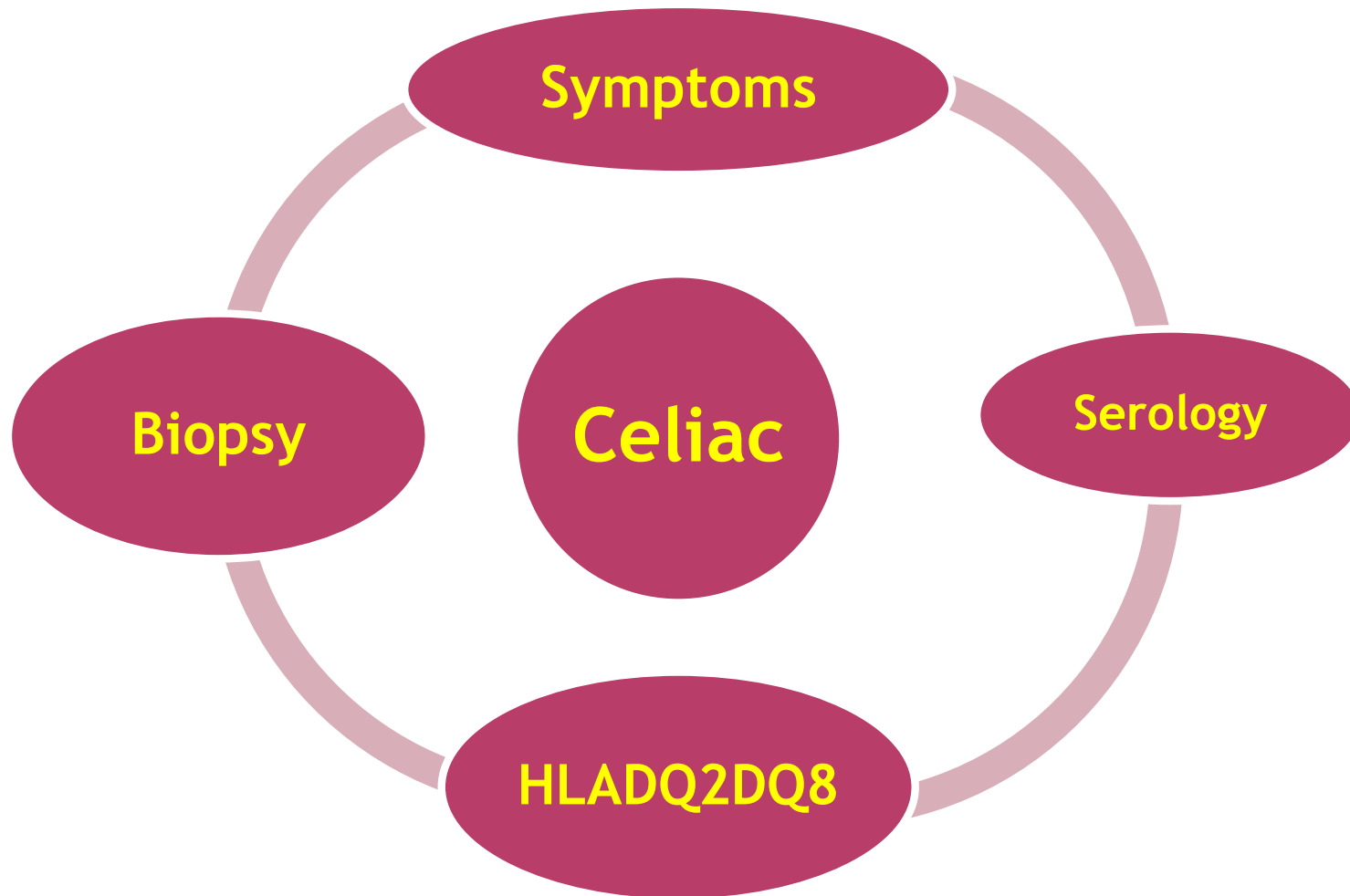
Or

- ◉ Non biopsy associated a high tTG-IgA (≥ 10 ULN) AND a positive anti-Endomyseal IgA & HLA (DQ2/DQ8)+



Extraintestinal
symptoms





GASTROINTESTINAL SYMPTOMS

- ◉ Chronic or recurrent & persistent diarrhea/Steatorrea
- ◉ Malabsorption(Bad or foul odor ,Pale,Greasy/Frothy)
- ◉ Poor weight gain /Weight loss/Muscle Atrophy
- ◉ Abdominal distension /Bloating/flatulence, and Paradoxical & chronic Constipation
- ◉ Vomiting/Nausea
- ◉ Symptoms suggestive for
 - Irritable bowel syndrome
 - Severe lactose intolerance
- ◉ Abnormal liver biochemical tests
- ◉ Primary Biliary Cirrhosis/Cryptogenic Cirrhosis
- ◉ Ascites due to Hypoproteinemia

Gastrointestinal



Extraintestinal symptoms



PSYCHIATRIC DISORDERS

- ◉ Chronic fatigue/
- ◉ Depression
- ◉ Bipolar disorder
- ◉ Apathy
- ◉ Excessive anxiety
- ◉ Schizophrenia
- ◉ Eating disorders
- ◉ ADHD Autism
- ◉ Sleep disturbances
- ◉ Anxiety disorders are usually reactive in patients with CeD and improve with a GFD. Depressive disturbances may significantly impair QoL and are a good predictor of lack of dietary compliance

Neurologic

- ◉ **Gluten neuropathy / idiopathic neuropathy**
- ◉ Symmetrical / Asymmetrical neuropathy
- ◉ Only 1/3 has enteropathy
- ◉ Effect of a GFD on peripheral neuropathy is disappointing
- ◉ **Gluten encephalopathy**
- ◉ **Temporal lobe epilepsy** with hippocampal sclerosis / Epilepsy with cerebral calcifications
- ◉ , gradually progressive neurological disease and gluten sensitivity associated with white matter lesions, **mimicking multiple sclerosis**, have been described.
- ◉ Mild cognitive symptoms called '**foggy brain**', which improves when gluten-restriction is started, but re-appears with dietary contamination
- ◉ Concentration and attention difficulties, episodic memory deficits, word-retrieval problems, reduced mental acuity and episodes of confusion or disorientation are common recognised features in CeD
- ◉ **nonhereditary Cerebellar ataxia**
- ◉ **Recurrent migraine headaches**

Non Classical symptoms

- Dental enamel hypoplasia of permanent teeth (symmetric distribution)
- Recurrent aphthous stomatitis
- Decreased bone mineralization /Repetitive fractures (not explained by the level of trauma)
- Osteopenia
- Skin** :Dermatitis herpetiformis -like rash
- Alopecia/Chronic Urticaria
- Erythema nodusom



Non Classical symptoms

- ◉ Arthritis or arthralgia (even if there is a presumed underlying rheumatic disease)
- ◉ Juvenile chronic arthritis
- ◉ **Endo:** Short stature or low height velocity
- ◉ Delayed puberty
- ◉ **OB/GYN**
- ◉ Recurrent fetal loss
- ◉ low birth weight infants
- ◉ Reduced fertility
- ◉ Amenorrhea



Hematology:

- ◉ Nutritional Anemia /Iron deficiency ,folate or vitamin B12 anemia often poorly responsive to supplementation

Dermatitis herpetiformis(DH):

- ◉ DH is the specific cutaneous manifestation of CeD. Both diseases occur in gluten sensitive individuals, share the same HLA haplotypes and improve following a GFD
- ◉ Histological changes similar to CeD enteropathy have been reported in 75% of patients with DH
- ◉ The remaining have minor changes consistent with possible latent CeD
- ◉ Minor GI complaints are the most common findings in DH
- ◉ Signs of malabsorption are rare.

WHOM TO TESTING

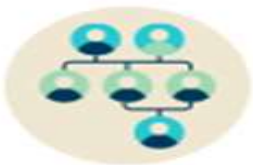
- ◉ Is recommended for patients :
- ◉ Suggestive symptoms
- ◉ Children in at risk groups regardless of symptoms

AT RISK GROUPS

(CONSISTENT WITH SEVERAL PEDIATRIC GUIDELINES)

- ◉ First & second-degree relatives of patients with celiac disease
- ◉ Autoimmune thyroiditis
- ◉ Cryptogenic Cirrhosis
- ◉ Type 1 diabetes
- ◉ Autoimmune liver disease
- ◉ Down syndrome
- ◉ Selective IgA deficiency
- ◉ Turner syndrome
- ◉ Williams syndrome
- ◉ Juvenile chronic & idiopathic arthritis

Specific
conditions



CONCLUSION

- ⊙ Performing test for **clinical judgment and at risk groups**
- ⊙ Screening is not recommended for asymptomatic patients who are not members of a high-risk group
- ⊙ Although **broad screening** might permit recognition and **correction of subclinical nutritional deficiency states**, resolution of mild symptoms, and, potentially, decreased risk for other complications it is also proposed that asymptomatic individuals may have difficulty adhering to dietary treatment

DIAGNOSTIC TESTING

Decisions about diagnostic testing should be based on symptoms, signs, and risk factors, without regard to the individual's country of origin, ancestry or race/ethnicity

Gluten exposure is essential for the development of CeD

Screening of the general population is not recommended

TESTING

- ◉ False-positive / False-negative
- ◉ Case reports suggest may be falsely elevated during a febrile illness
- ◉ **Gluten exposure is essential** for the development of CeD. Upon ingestion, gluten peptides resist complete digestion in the gastrointestinal tract, leading to the formation of immunogenic peptides
- ◉ **Pretesting diet**
 - ◉ To perform while on a gluten-containing diet.
 - ◉ To start on a gluten-free diet without prior testing should resume a diet containing ideally **at least 3 g gluten/day** (one slice of bread daily) for at **least 6 weeks** before undergoing antibody testing
- ◉ Serologies may become negative within weeks of beginning a gluten-free diet but may take up to a year or even longer in some cases .

Trigger

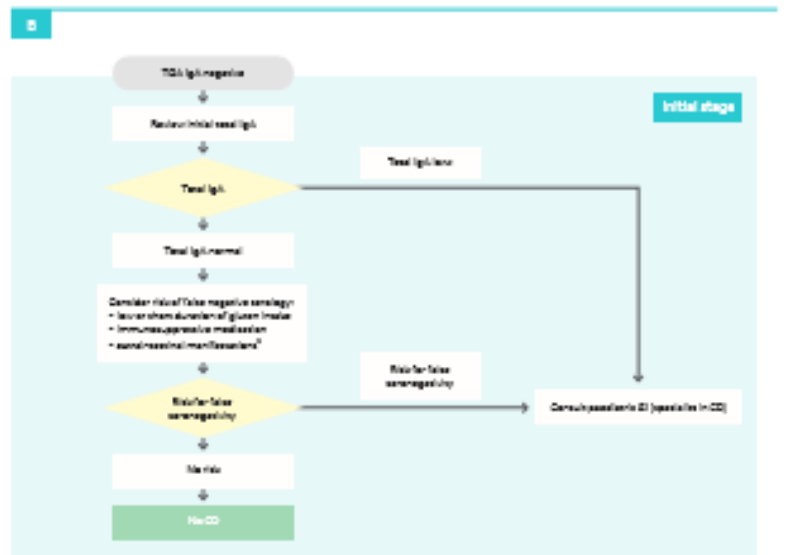
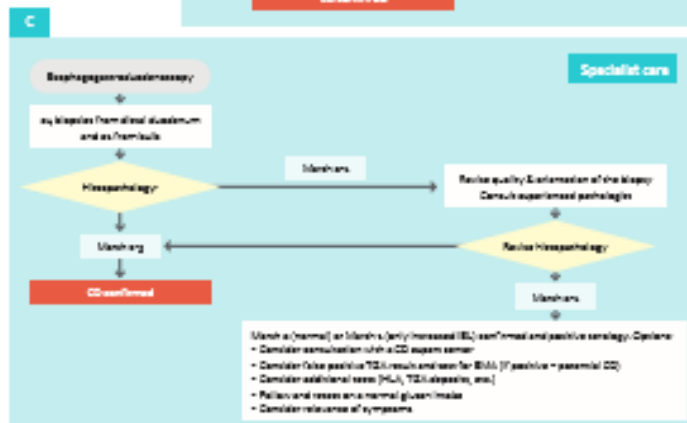
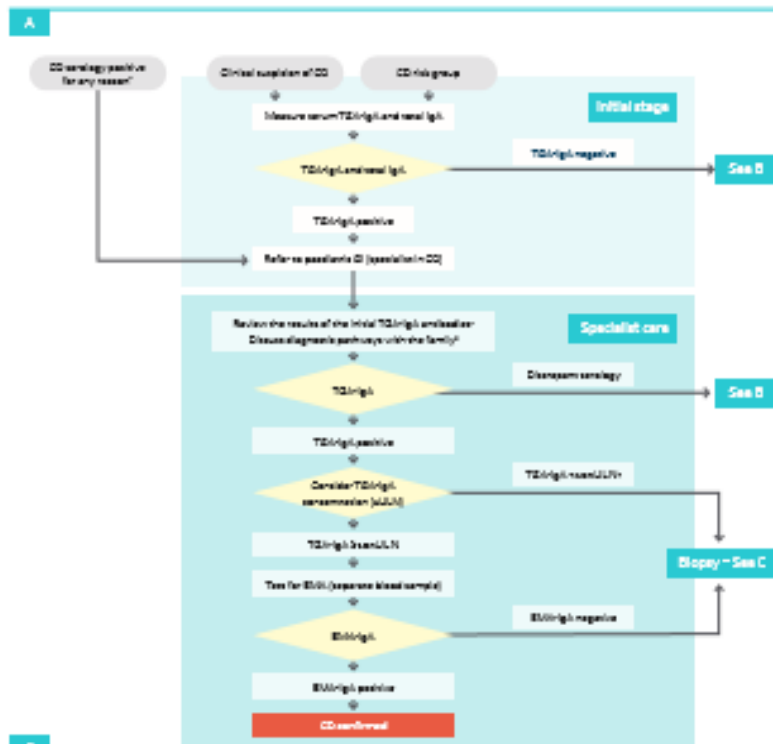
- ⊙ Major stress
- ⊙ Viral infection
- ⊙ Medication (alfa interferon)
- ⊙ Pregnancy
- ⊙ Surgery
- ⊙ Hepatitis B Vaccine

- ⊙ Gut microbium

ROLE OF PROBIOTICS

- ◉ Gut microbiome composition might differ in individuals with celiac disease compared to healthy people
- ◉ *Yersinia enterocolitica* , *Escherichia coli*, *Pseudomonas aeruginosa* it was found that this bacterium has **proteins similar to gluten**
- ◉ might trigger an immune response in some people, leading to **cross-reactivity/leaky gut**
- ◉ Decrease in bacteria like **Bifidobacterium** or **Lactobacillus** species have proteolytic activity against gluten, which could be protective
- ◉ **Early exposure to certain bacteria might influence the development of celiac disease**
- ◉ **Gut dysbiosis**, promoting **inflammation and immune dysregulation.**
- ◉ Exposure to pathogens like **Rotavirus or Giardia lamblia** in infancy has been hypothesized to increase celiac risk, possibly by priming the immune system

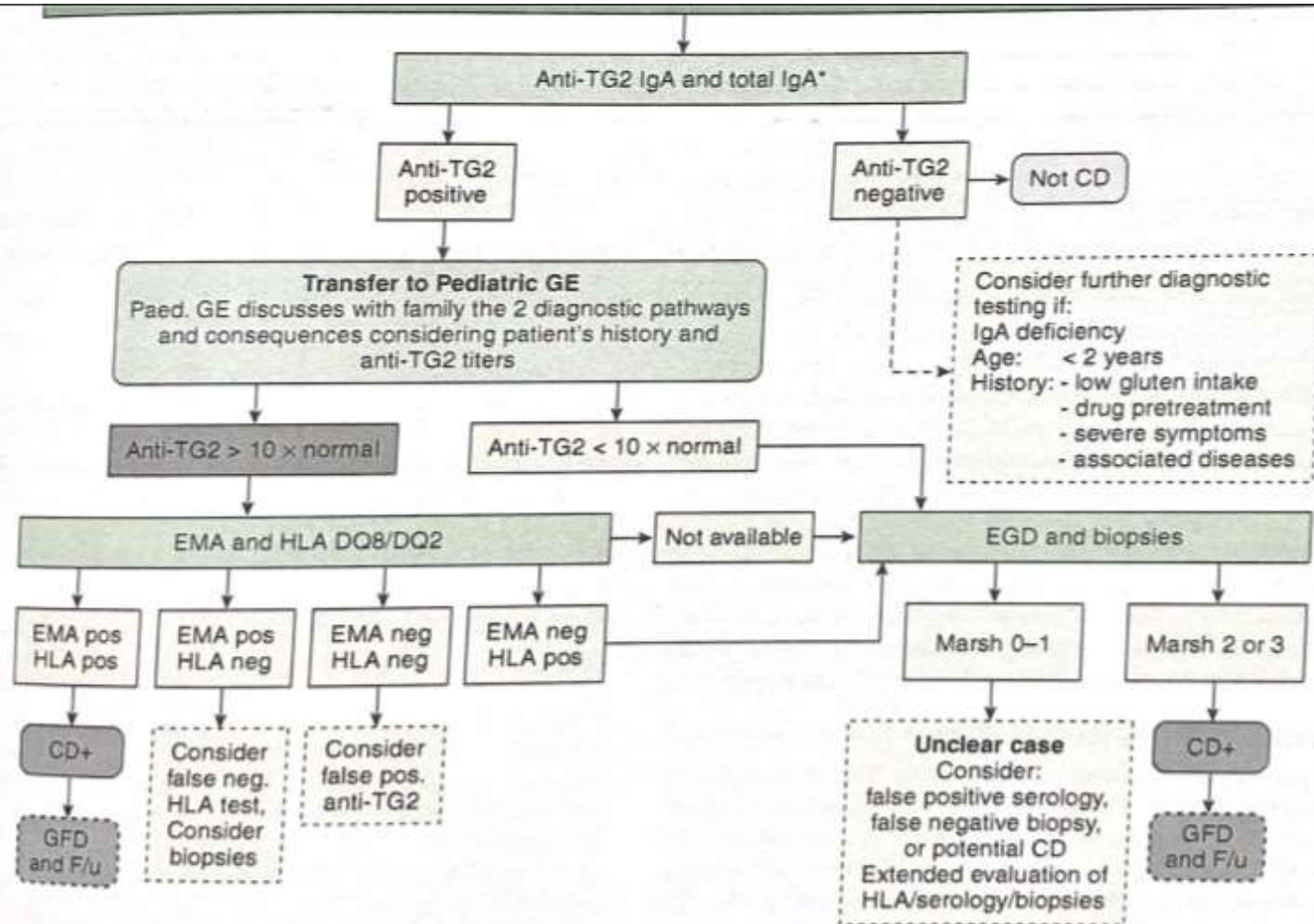
New Guidelines for the Diagnosis of Paediatric Coeliac Disease



Healthcare

[illegible]

CHILD / ADOLESCENCE WITH SYMPTOMS SUGGESTIVE OF CD



Anti TTG IgA/Total IgA

⊙ Anti TTG + <10xNormal  Biopsy

EMA/HLA Not available  Biopsy

⊙ Anti TTG + >10xNormal

⊙ **EMA/HLA**

⊙ EMA+/HLA+



CD+/GFD&FU

⊙ EMA+/HLA-



False Neg HLA/Biopsy

⊙ EMA-/HLA-



False +TTG

EMA-/HLA+



Biopsy

TTG<10/EMA-HLA-/No available
(**Biopsy**)

⊙ Anti TTG -  **CD-**

⊙ **TTG IgA-**



⊙ further Diagnostic

⊙ IgA deficiency

⊙ Less than 2 years

⊙ Low gluten intake

⊙ Severe Symptoms

⊙ Drug pretreatment

⊙ Associated Disease

Anti TTg IgG

- ◉ Anti-TTG IgG **isn't a first-line test**
- ◉ Where IgA levels are low, IgG might be more informative.
- ◉ The presence of Anti-TTG IgG **alone isn't sufficient for diagnosis.**
- ◉ It needs to be **combined with other tests like EMA (endomysial antibodies) IgA, genetic testing (HLA-DQ2/DQ8), and confirmatory biopsy.**
- ◉ In **IgA-deficient** individuals, anti-tTG IgA tests may yield false negatives , so **anti-tTG IgG or deamidated gliadin peptide (DGP) IgG tests are used instead.**
- ◉ False Positives/Negatives :
- ◉ More likely in IgG testing due to cross-reactivity with other conditions (e.g., liver disease, infections) or milder disease forms.

METHOD OF SCREENING AT HIGH-RISK GROUPS

- ◉ For asymptomatic individuals
- ◉ First performing test **at three years of age or older**
- ◉ (On a gluten-containing diet for at least one year)
- ◉ **Initial results negative**, screening tests should be repeated at intervals or at any time that symptoms develop.
- ◉ The optimal time interval for subsequent testing has not been studied, but, in our practice, we screen asymptomatic members of these groups approximately **every three years during childhood or up to annually if other blood work is being obtained**, as well as when symptoms are concerning for celiac disease

HLA TYPING

- ◉ HLA DQ2 90-95%
- ◉ HLA DQ8 5%
- ◉ HLA Neg 2%
- ◉ HLA (one or two) 1/3 of normal population
- ◉ Useful tool for exclude of CD or unlikely
- ◉ Offer for asymptomatic at risk group
- ◉ (**Except of type 1 diabetes**)

SUGGESTIVE OF CD

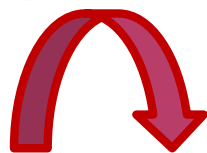
- Bulb 2 sample & D2 4 sample
- A correctly orientated biopsy
- **↑25/100** IEL intraepithelial Lymphocyte
- Villous to crypt ratio of <2



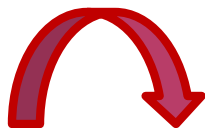
Endoscopy/Biopsy/Marsh Classification

⊙ Marsh 0 — I

⊙ Unclear Case



False Serology/False Biopsy
Or Potential CD



HLA/Serology/Re
Biopsy

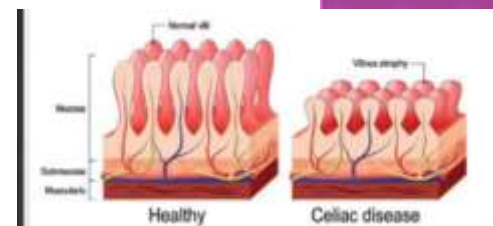
⊙ Marsh II or III



CD



GFD/FU



D/D

- ◉ Food allergy
- ◉ Non Celiac gluten sensitivity
- ◉ Post infectious Diarrhea
- ◉ Crohn disease
- ◉ Primary lactose intolerance
- ◉ Functional abdominal pain
- ◉ IBS
- ◉ Immunodeficiencies
- ◉ Graft versus host disease
- ◉ H pylori infection/Giardiasis



MANAGEMENT OF CD

Life long GFD / **Micronutrients** & **Macronutrient** support (Iron/ca/Mg/Zinc/Folat/Niacin/Riboflovin/B12 /D/**Cu&B6**)

- ◉ Follow up of **Symptomatic improvement**/ IgA-TGA acts as a surrogate marker for healing of the small-bowel mucosa
- ◉ Should be performed every **6 Mo** until normalization
- ◉ (Normalization time based on titer and histologic damage at time of diagnosis **3-6-24** mo) / Then every 12-24 month thereafter.

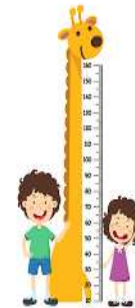
IT IS GENERALLY ACCEPTED THAT CLINICAL FOLLOW-UP OF CHILDREN AND ADOLESCENTS WITH CELIAC DISEASE FOLLOW UP

Follow-up and monitoring Is necessary:

To assess growth and development

Resolution of their symptoms and possible complications(Long-term complications Prevent **growth failure**,**Premature Osteoporosis infertility & Malignancy**

Monitor compliance to the treatment (GFD)



Nonresponsive (Unintentional gluten contamination)
Refractory CeD)

The current follow-up approach is based on local practice and opinion with lack of evidence-based approaches. following-up their patients and **offered scope for improvement**

In a study from an era in which celiac disease was not treated, mortality was 12 percent

NON RESPONSE CD

- ◉ **Accidental exposure**
- ◉ **IBS**
- ◉ **Bacterial Over Growth**
- ◉ **Refractory CD**
- ◉ **Role of Genotyping**
- ◉ **Genetic complexity beyond HLA**
- ◉ **Non HLA Gene (IL5/RGS1)**
- ◉ **Mass spectrometry for gluten**

POTENTIAL CELIAC DISEASE

- Patients with positive TGA-IgA and EMA and no or minor small bowel histological changes are usually diagnosed as having ‘potential’ CD.
- To low gluten intake prior to biopsies,
- Sampling error or incorrect orientation of the biopsies for reading so these should be checked before diagnosing ‘potential’ vs ‘true’ CD.
- Once confirmed, potential CD requires clinical and laboratory surveillance (serology, further biopsies) to monitor possible evolution to villous atrophy and referral to a center with expertise in CD for follow-up.

NCGS

- ◉ Gluten-related symptoms without meeting criteria for celiac disease or wheat allergy
- ◉ Self-diagnosis
- ◉ Adult/ lacking data in kids
- ◉ By exclusion
- ◉ Normal serology
- ◉ Normal Biopsy
- ◉ Temporary gluten avoidance



Improvement

The ESPGHAN QoC Survey identified gaps between clinical practice and guideline recommendations.

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ORIGINAL ARTICLE

Gastroenterology: Celiac Disease

Celiac disease diagnosis in clinical practice: ESPGHAN quality of care survey from 129 pediatric hospitals across 28 countries

WHO QualitQoCy-of-Care (QoC)

- ◉ (ESPGHAN) guidelines recommend first-line serology for (CeD), measuring only transglutaminase antibodies (TGAimmunoglobulin A [IgA]) plus total IgA. If TGA-IgA is ≥ 10 times the normal value, pediatric gastroenterologists (pedGI) may diagnose CeD without biopsies if autoantibodies against Endomysial Ab (EMA-IgA) are positive in a 2nd blood sample.
- ◉ This (QoC) project benchmarked diagnostic workup in clinical practice using ESPGHAN CeD guidelines as reference.
- ◉ A pseudonymized survey on CeD practices was sent to 141 hospitals within the ESPGHAN QoC-network in 28 countries

WHO Quality-of-Care (QoC)

- Questionnaires were completed by 129/141 (91.5%) hospitals, with 121 (94%) having ped GI staff.
- As reasons conflicting with good QoC for CeD in their setting, responders assumed knowledge deficits among the public (57%), primary care providers (64%), non-GI physicians (16%), and pedGIs (0%). For initial testing, **66% of physicians ordered only total IgA and TGA-IgA, 7% did not use this combination,**
- And 29% ordered additional serology (TGA-IgG, EMA, antibodies against deaminated gliadin peptide, or native gliadin).
- Regarding conflicting results for TGA-IgA and histopathology in IgA-sufficient children,
- 61% incorrectly classified negative TGA-IgA with Marsh 2 and 57% with Marsh 3 lesions as “potential CeD,”
- while 49% excluded CeD in the case of villous atrophy and negative TGA-IgA. Routine practice did not align with the ESPGHAN recommendations regarding performance of duodenal biopsies (27%), EMA-testing (34%), and diagnosis of CeD in IgA-deficient children (32%).
Conclusions: We identified areas for improving QoC regarding both effectiveness and efficacy, in pediatric patients with suspected CeD, and consequently developed **easy-to-use tools** to improve guideline implementation.

◉ What is Known

- ◉ The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) provides guidelines for celiac disease diagnosis in children. • **To ensure WHO Quality-of-Care (QoC) standards, the diagnostic process should be effective, safe, and efficient, to optimize resource use and reduce burden and costs**

◉ What is New

- ◉ The ESPGHAN QoC Survey identified **gaps between clinical practice and guideline recommendations**. • Nearly **one-third of hospitals order unnecessary first-line serological tests, hence increasing costs without improving care**. • Physicians misinterpreted different combinations of serology and histopathology results, leading to under- and over-diagnosis of “celiac disease” and “potential celiac disease.” • **Pediatric gastroenterologists overestimate their knowledge compared to their true diagnostic performance.**

WHO QUALITY-OF-CARE (QOC)

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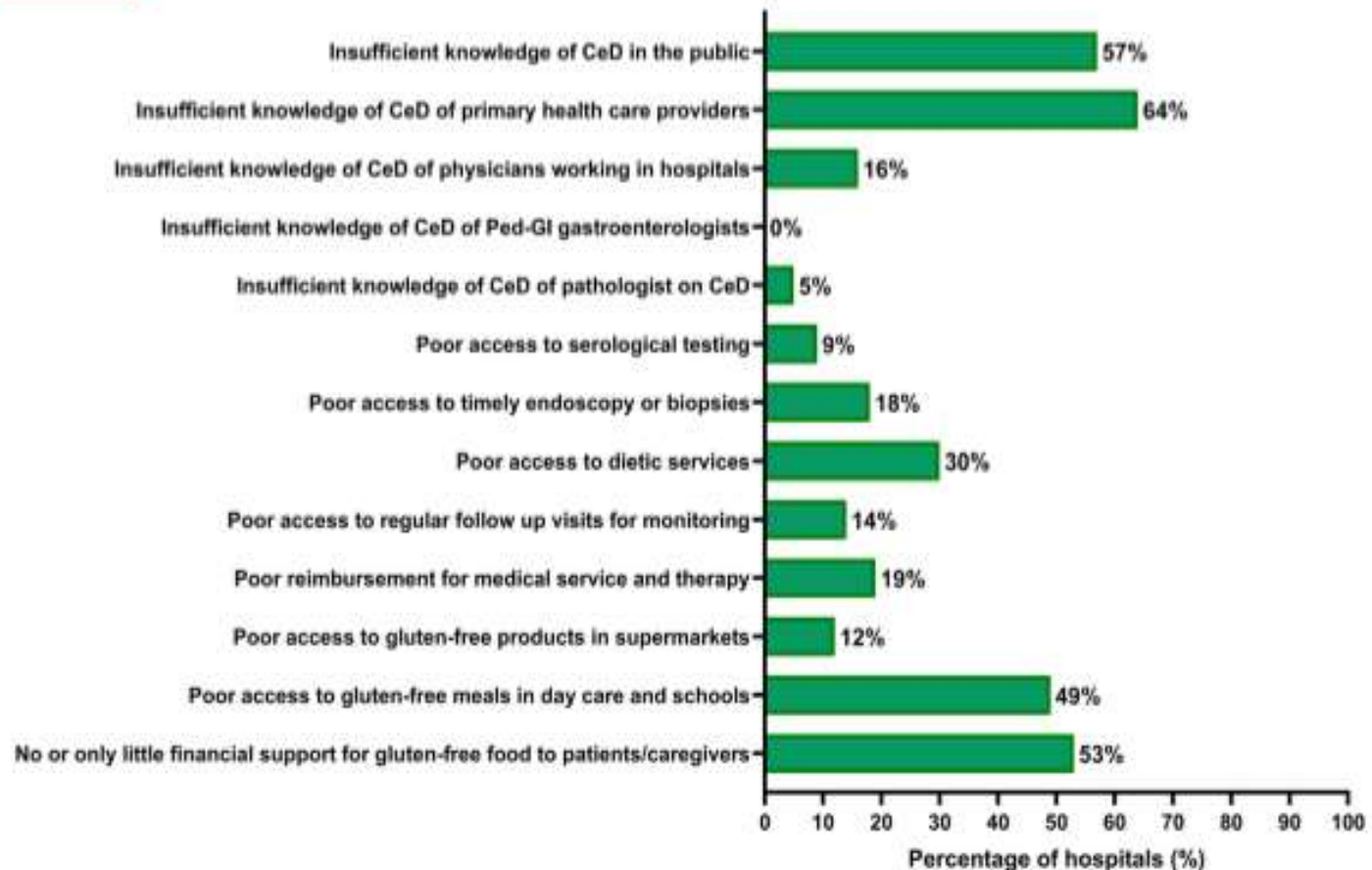


FIGURE 1 Answers to the question: "Where do you see deficits in your setting conflicting with good Quality-of-Care in pediatric patients with celiac disease?" (*N* = 129).

FUTURE DIRECTIONS

- ⦿ Encourage multidisciplinary approach
 - ⦿ Expert team/ Opinion
 - ⦿ Refer patients appropriately
 - ⦿ Provide proper patient education
 - ⦿ Pay attention in Biopsy samples
- (Capsule Endoscopy)**
- ⦿ Staying updated on evolving guidelines
 - ⦿ Emerging therapies(Glutenases /Vaccines

Thank you for your attention

