COELIAC DISEASE
RECENT ADVANCES

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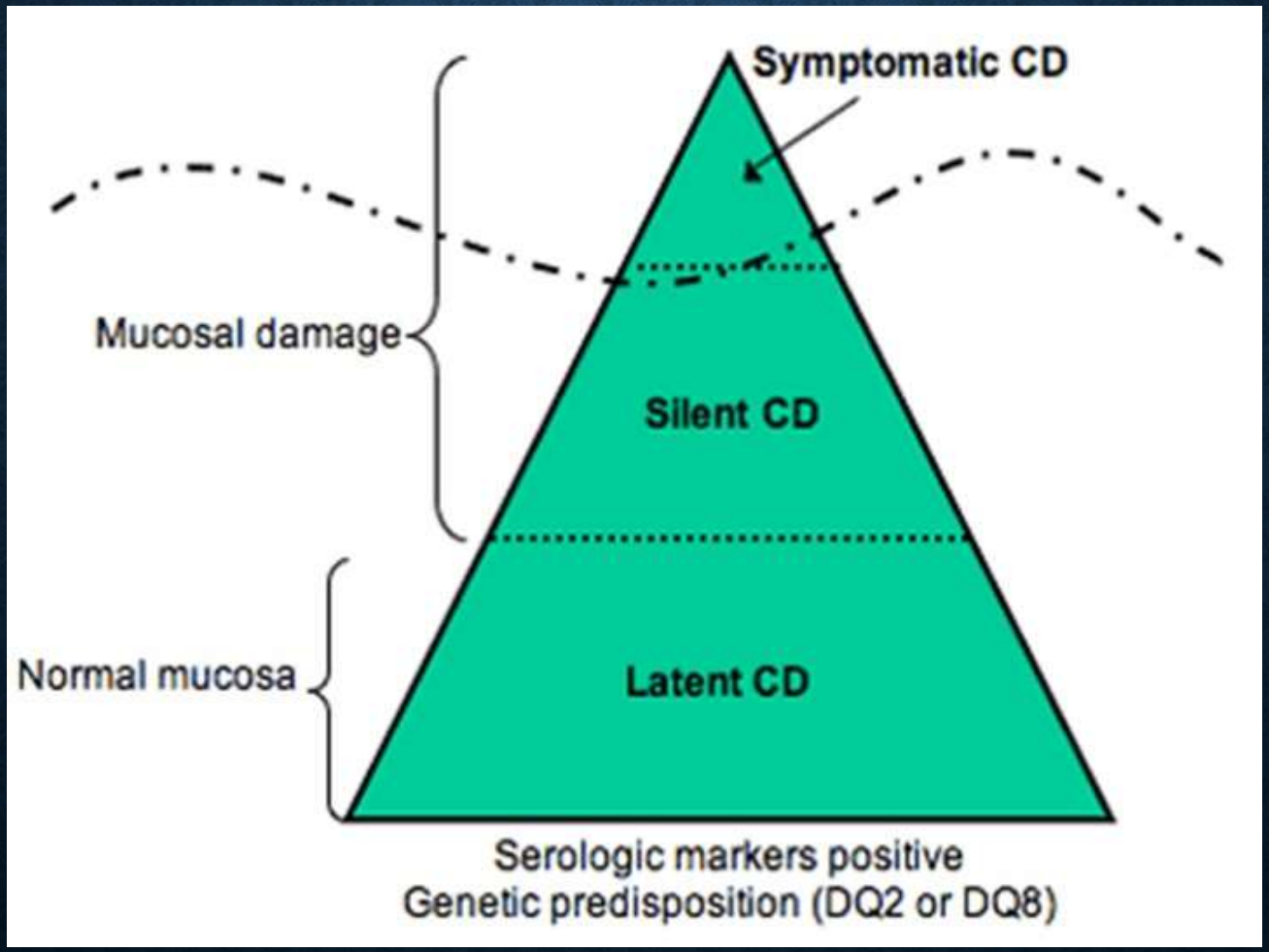
COELIAC DISEASE

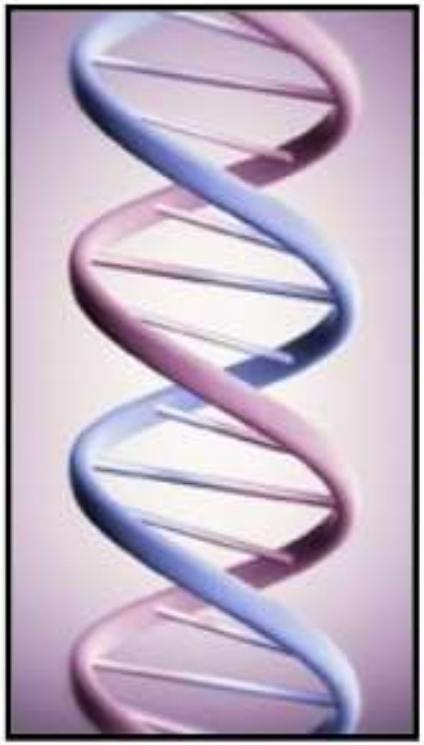
- Inflammatory autoimmune disease targeting the small intestine associated with production of autoantibodies.
- Triggered by Gluten in genetically susceptible individual.
- Pro-inflammatory immune reaction within small intestine leads to damage and atrophy of intestinal villi.

HISTORICAL ASPECTS

- 2,000 yrs ago, a Greek physician named ***Aretaeus the Cappadocian*** provided the 1st known description of adult patients with celiac disease. The name ***'celiac'*** is derived from the Greek for ***'suffering in the bowels'.***
- In October 5, 1887, ***Dr. Samuel Gee***, an English Medical Lecturer gave to medical students a lecture on the 'celiac affection' & this constitutes the modern 'rediscovery' of celiac disease.

THE COELIAC ICEBERG





- ***Genetic predisposition***

  HLA-DQ(DQ2 &/or DQ8) genes

- ***Environmental trigger***
  - Dietary
  - Non-dietary??

FACTORS ASSOCIATED WITH DEVELOPMENT OF CELIAC DISEASE

Genetic component

- Increased risk for family members
- Prevalence of 10% in first-degree relatives
- Known genetic association

HLA-DQ2 • HLA-DQ8

Environmental component

- Ingestion of cereal grain proteins
- Wheat
- Barley
- Rye
- Collectively referred to as gluten

Pathophysiology

Environmental triggers

Cereals containing toxic proteins for patients (gliadin, secalin , hordein)

Celiac disease

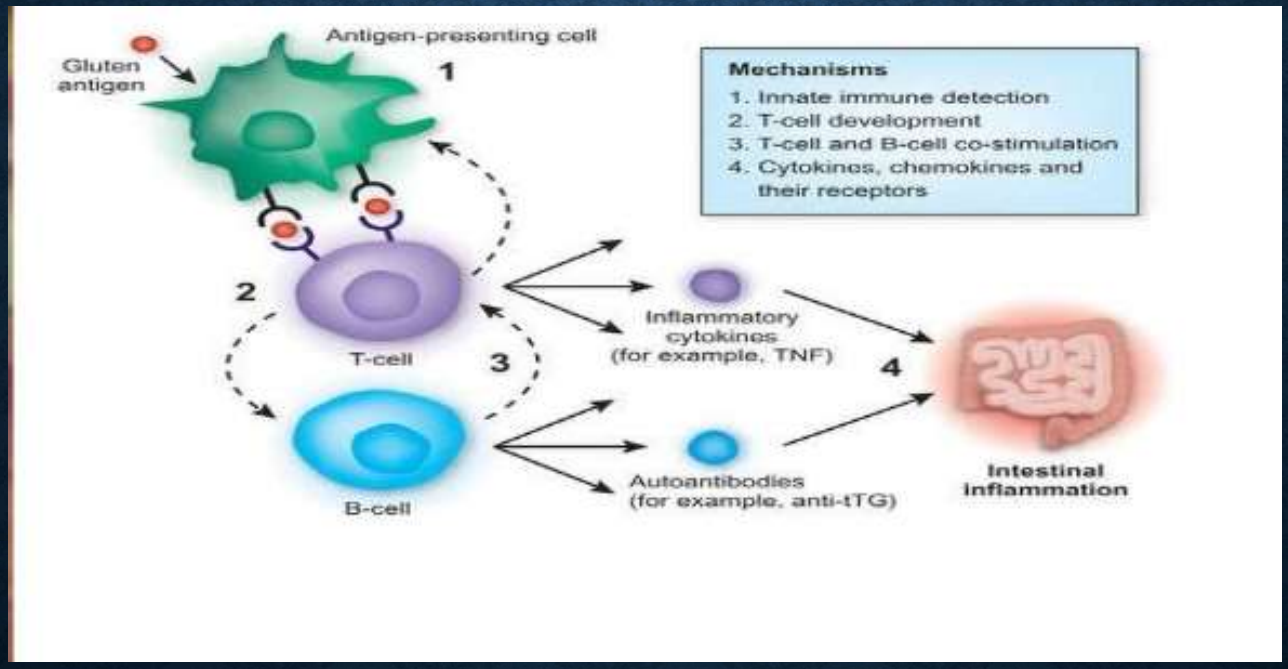
Genetic predisposition

DQ2 and/or DQ8 positive HLA haplotype

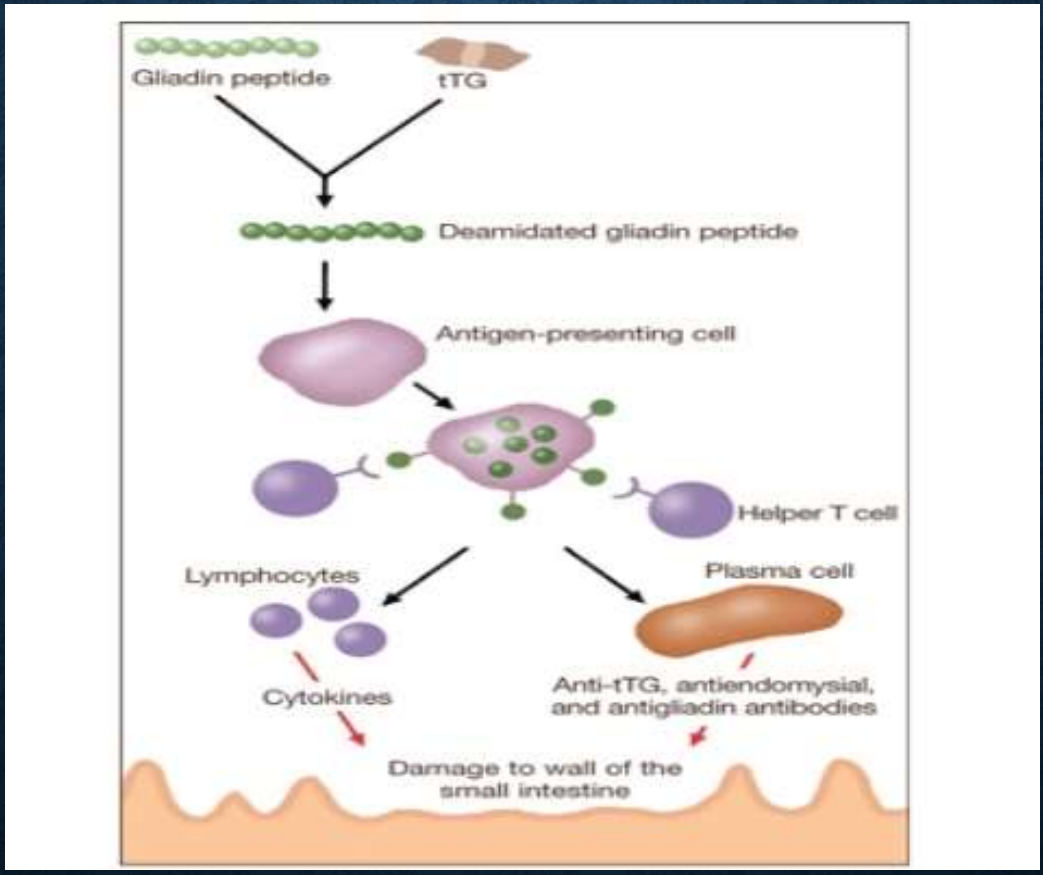
Immune System

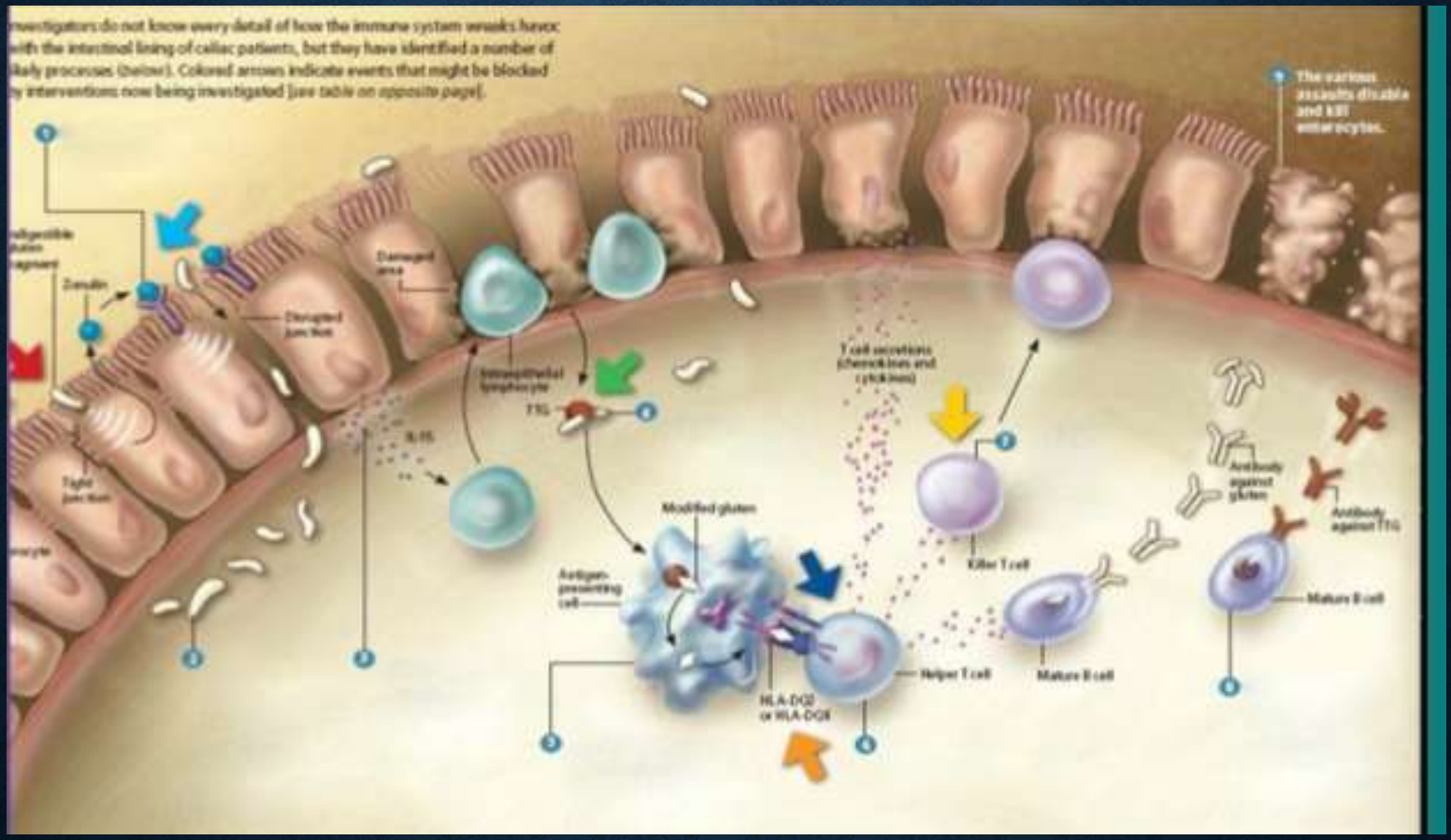
Autoimmunity due to the loss of the mucosal barrier function

MECHANISM OF COELIAC DISEASE PRODUCTION

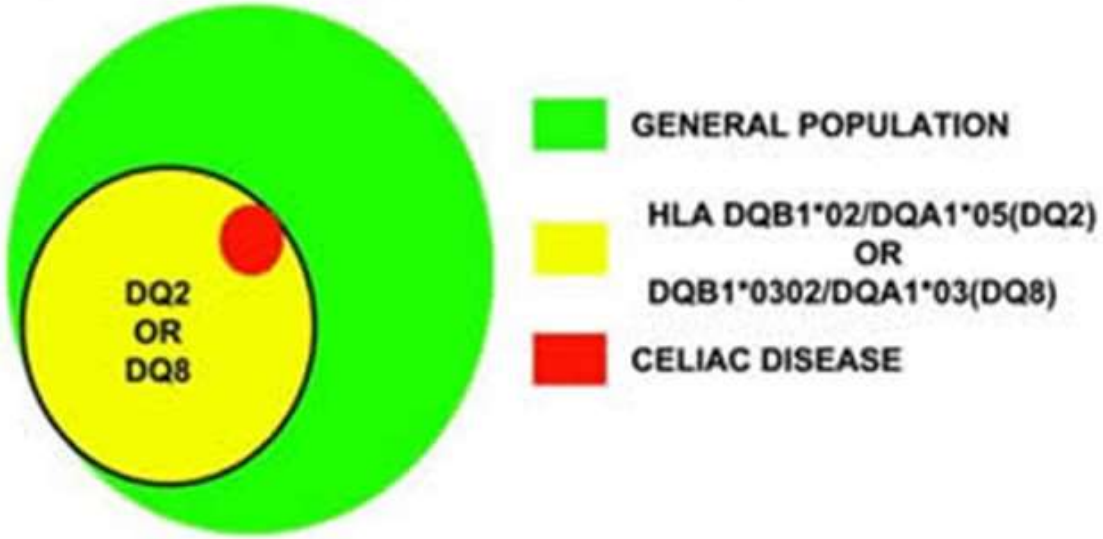


IMMUNE RESPONSE IN CELIAC DISEASE




Modified gluten
Killer T cell
Helper T cell
Mature B cell
HLA-DQ2
or HLA-DQ8

Celiac Disease and HLA Risk



GENETICS

The receptors formed by these genes binds to gliadin peptides more tightly than other forms of the antigen presenting receptor.

PROLAMINE

The majority responsible storage protiens rich in prolamine and glutamine. It disrupt tight junctions between enterocytes which allow large amino acids to enter circulation and stimulate immune response.

TISSUE TRANSGLUTAMINASE

It modifies gluten peptides into a form that may stimulate the immune system more effectively.

VILLOUS ATROPHY AND MALABSORPTION

- The inflammatory process, mediated by T cells, leads to disruption of structure and function of small bowel's mucosal linning resulting malabsorption of nutrients, minerals and fat soluble vitamins A,D,E,K from food.
- Lactose intolerance may be present due to decreased bowel surface and reduced production of lactase.
- Proximal intestine is more severely involved.
- Decreased enzyme like disaccharidase, peptidase, alkaline phosphatase, ATPase and esterase.

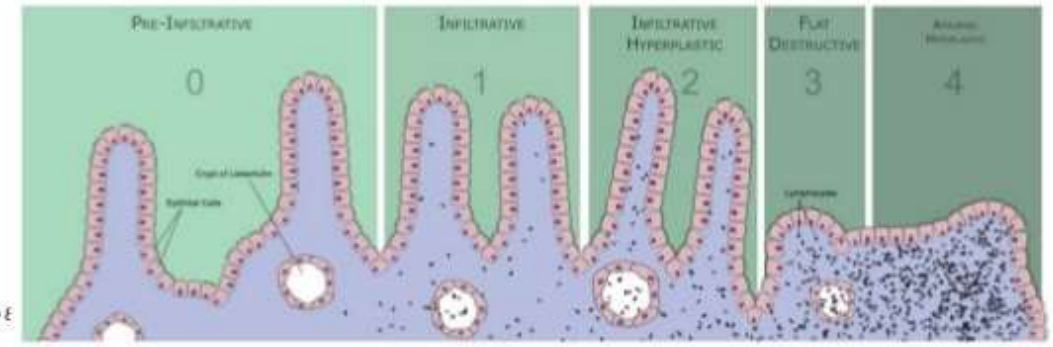
RISK MODIFIERS

- Infection by Rota virus
- Human Intestinal Adeno virus
- Smoking is protective against adult onset coeliac disease
- Timing of exposure to gluten in childhood is important risk modifier
- Prolonging breast feeding until introduction of gluten containing grains into diet is associated with 52% reduced risk of developing coeliac disease in infancy

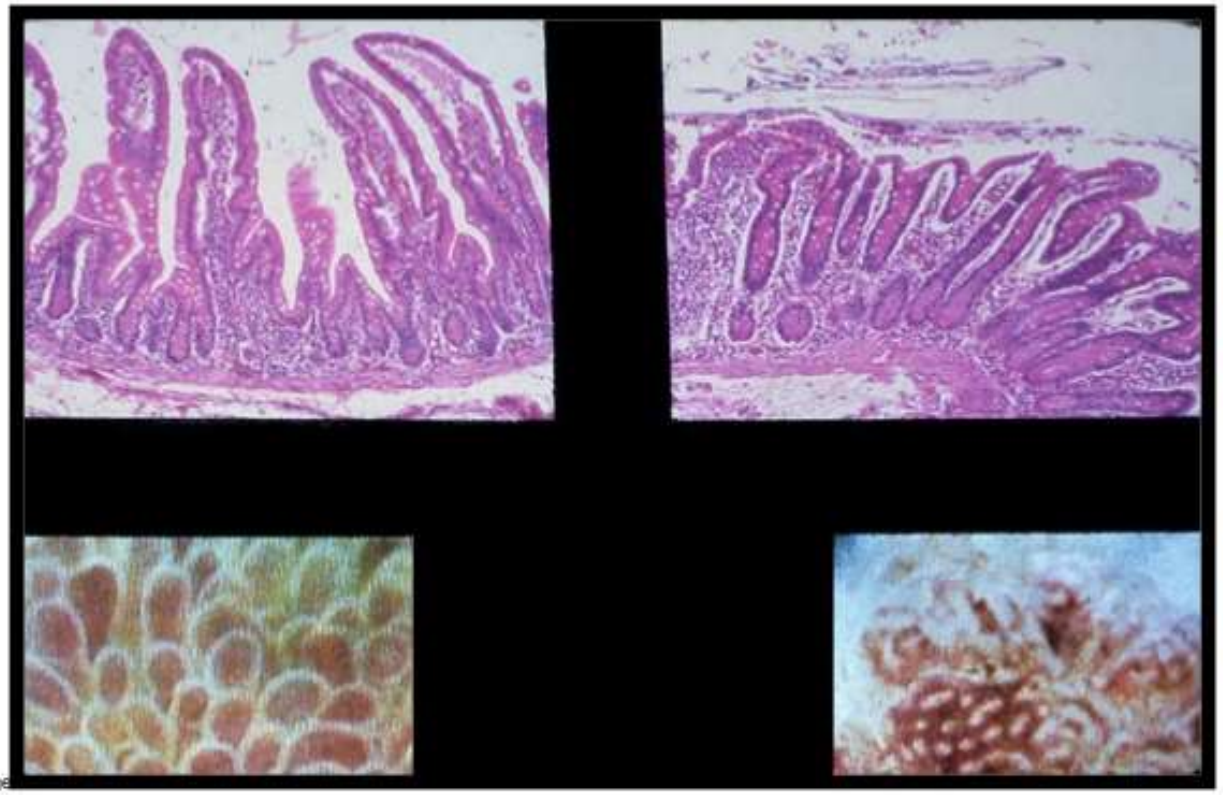
PATHOLOGICAL SPECTRUM OF COELIAC DISEASE

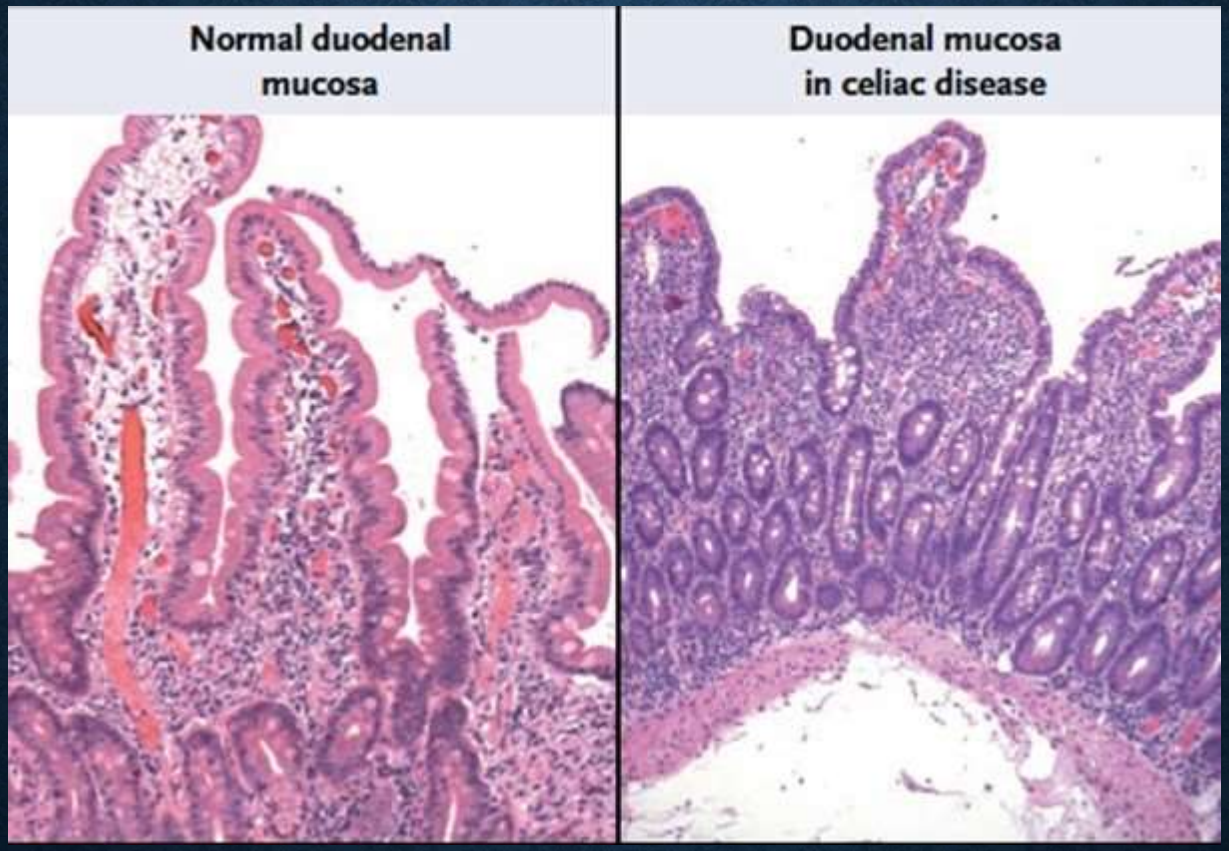
The classic pathology changes of celiac disease in the small bowel are categorized by ***"Marsh Classification"***:

- ***Marsh stage 0:*** normal mucosa
- ***Marsh stage 1:*** ↑ intra-epithelial lymphocytes >20/100 enterocytes
- ***Marsh stage 2:*** proliferation of the crypts of Lieberkuhn
- ***Marsh stage 3:*** partial or complete villous atrophy
- ***Marsh stage 4:*** hypoplasia of the small bowel architecture



PATHOLOGY OF COELIAC DISEASE




Normal duodenal mucosa
Duodenal mucosa in celiac disease

The most commonly recognized symptoms of celiac disease relate to the improper absorption of food in the GIT.

Patient presents with ***diarrhea (<50%)***, ***steatorrhea***, ***flatulence***, ***distended abdomen***, ***weight loss***, & ***generalized weakness.***

Up to ***38 %*** of patients are ***asymptomatic.***

Unrecognized celiac disease may cause ***malabsorption***, ***iron deficiency anemia***, ***osteoporosis***, ***osteomalacia*** causing bone fractures, pain & bony deformities.

People with celiac disease may also experience ***lactose intolerance*** due to ***lactase enzyme deficiency.***

CLINICAL MANIFESTATIONS OF COELIAC DISEASE

Gastrointestinal

- Diarrhea
- Weight loss
- Steatorrhea
- Abdominal pain
- Bloating
- Constipation
- Nausea

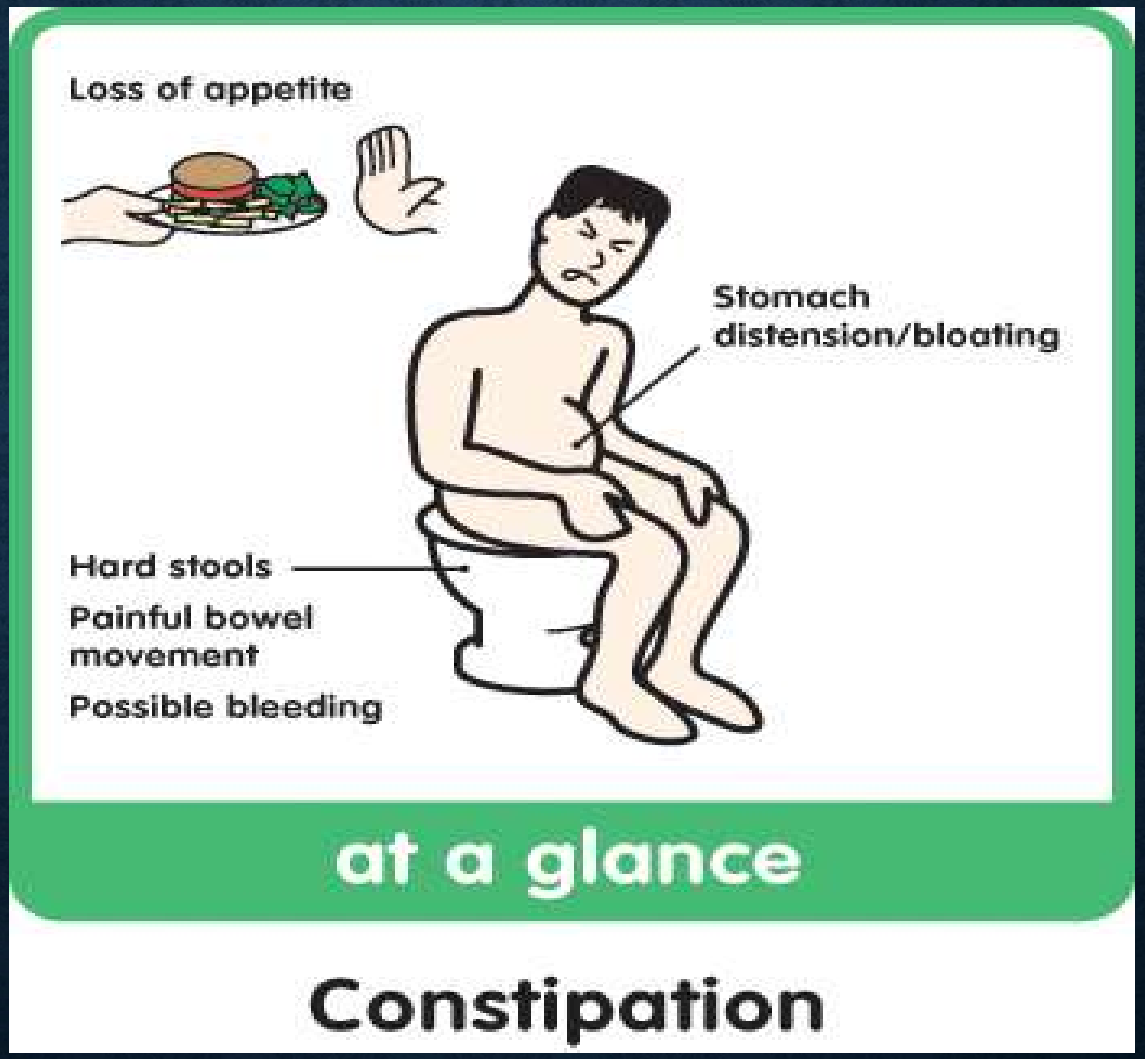
Malabsorption

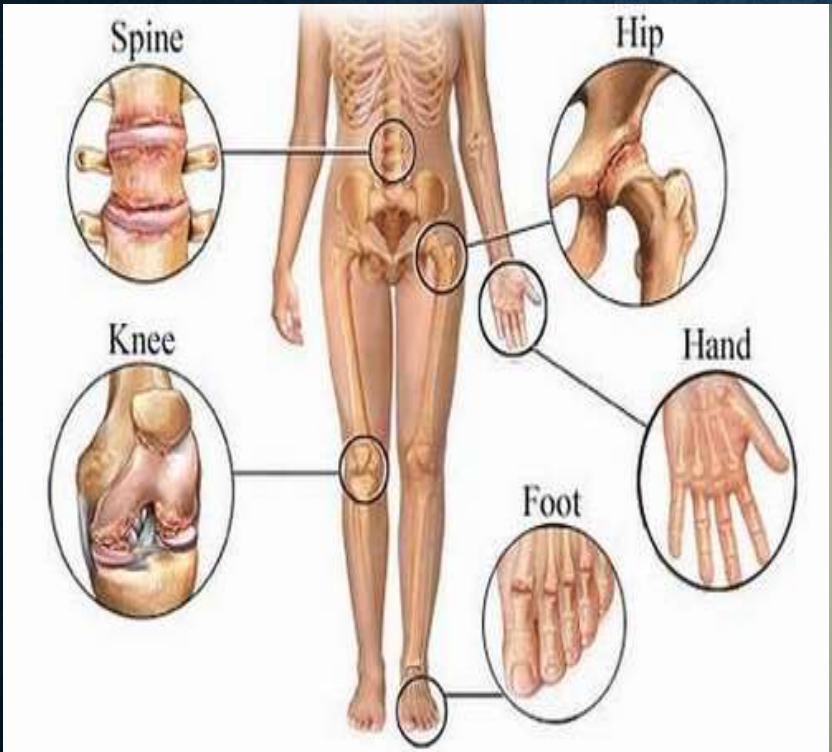
- Fe-deficient anemia
- B12 deficiency
- Folate deficiency
- Hypoproteinemia
- Hypocalcemia

Extra-GI

- Ataxia
- Infertility
- Arthralgias
- Dermatitis herpetiformis
- Hyposplenism

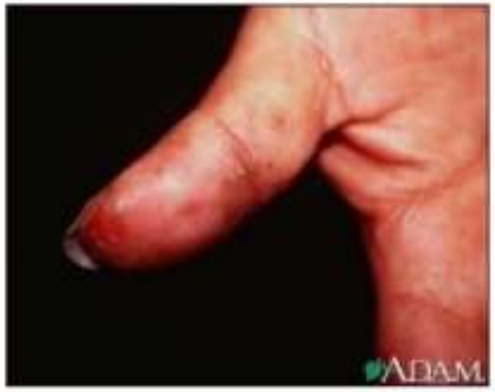
Other autoimmune conditions

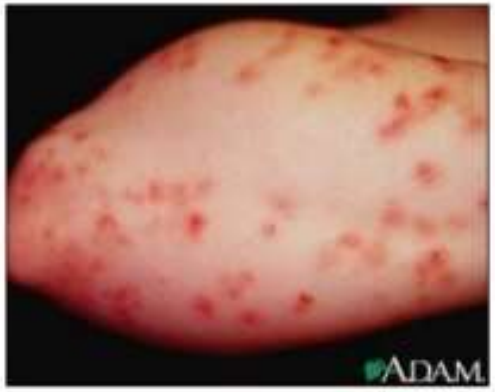

Loss of appetite
Stomach distension/bloating
Hard stools
Painful bowel movement
Possible bleeding
at a glance
Constipation

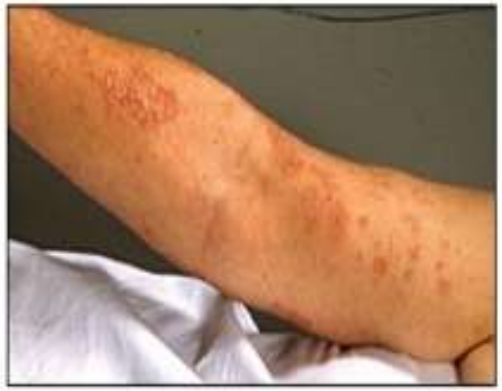

Spine
Hip
Knee
Hand
Foot

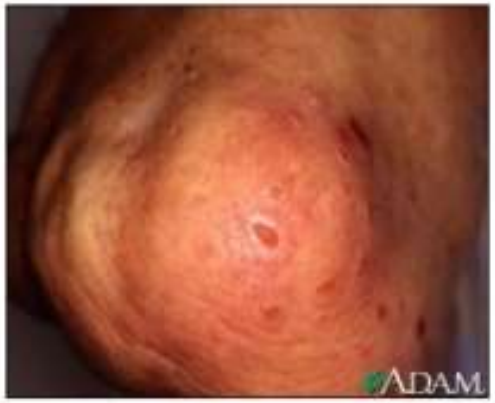
Extra-Intestinal manifestations of celiac disease

- Dermatitis Herpetiformis and other skin disorders
- Dental enamel hypoplasia
- Osteopenia/Osteoporosis
- Short Stature
- Delayed Puberty
- Iron-deficient anemia resistant to oral Fe
- Liver and biliary tract disease
- Arthritis
- Neurological problems
  - Ataxia
  - Peripheral neuropathy
  - Epilepsy
- Psychiatric Disorders
- Women Sub-In-fertility
  - Miscarriages
  - Low birth weight babies


A.D.A.M.


A.D.A.M.




A.D.A.M.

Dermatitis herpetiformis (DH) is the skin manifestation of celiac disease.

It is an ***intensely itchy rash*** that occurs in the hands, fingers, forearms, buttocks or scalp or anywhere on the body.

The rash typically consists of intensely itchy, small red dots that may develop into blisters or pimples.

Approximately ***10%*** of patients with celiac disease have DH, & it is estimated that **> *85%*** of patients with DH have celiac disease .

- “Coeliac disease is a food allergy or food intolerance issue”.
- “If you have diarrhoea or are constipated, then you must have coeliac disease”.
- Coeliac disease only affects people who are adults”.
- People can ‘grow out’ of the disease and is often only a temporary disease”.
- You have to be underweight to be diagnosed with coeliac disease”.

- In fact, the condition is an autoimmune disease.
- In fact, coeliac disease can really affect anywhere in the body and the sore stomach can be something totally unrelated to coeliac disease.
- In fact, coeliac disease can, and does, affect people from babies to the elderly.
- In fact, coeliac disease is a lifelong condition and it doesn't 'just go away' after diagnosis.
- In fact, people who are underweight, overweight and optimum (perfect) weight can get the disease.

DIFFERENTIAL DIAGNOSIS

- Anorexia nervosa
- Autoimmune enteropathy
- Bacterial overgrowth
- Collagenous sprue
- Crohn's disease
- Human immunodeficiency virus enteropathy
- Infective gastroenteritis
- Irritable bowel syndrome
- Ischemic enteritis
- Lactose intolerance
- Pancreatic insufficiency
- Soy protein intolerance
- Intestinal lymphoma

DIAGNOSIS OF CELIAC DISEASE

Initial diagnosis

- Evaluation of history
- Positive antibody serology
- Intestinal biopsy with characteristics of villous atrophy

Definitive diagnosis

- Resolution of clinical symptoms after initiation of gluten-free diet
- Generally accompanied by conversion to negative serology and reconstitution of intestinal villi

DIAGNOSIS OF CELIAC DISEASE

Serologic tests

- Antiendomysial antibodies
- Tissue transglutaminase antibodies
- Gliadin antibodies
- Unmodified gliadin antigen
- Deamidated gliadin antigen

Genetic tests

- HLA-DQ2 and HLA-DQ8

INVESTIGATIONS FOR EVALUATION OF MALABSORPTION

- CBC
- Serum calcium
- Total protein
- Serum albumin
- Vitamin D level
- Serum magnesium
- Serum IgA level
- BMD

Selective IgA deficiency

- Defined as absence of IgA in presence of normal IgG and IgM production
- More common in patients with celiac disease compared to general population
- IgA isotype for celiac-specific serologies more sensitive and specific compared to IgG isotype

Effect of gluten-free diet

- Down regulation of inflammatory immune response
- Reduction in autoantibody production

GENETIC TESTING FOR CELIAC DISEASE

- HLA-DQ2 • Present in 90% to 95% of patients with celiac disease
- HLA-DQ8 • Present in 5% to 10% of patients with celiac disease

HLA genetic typing

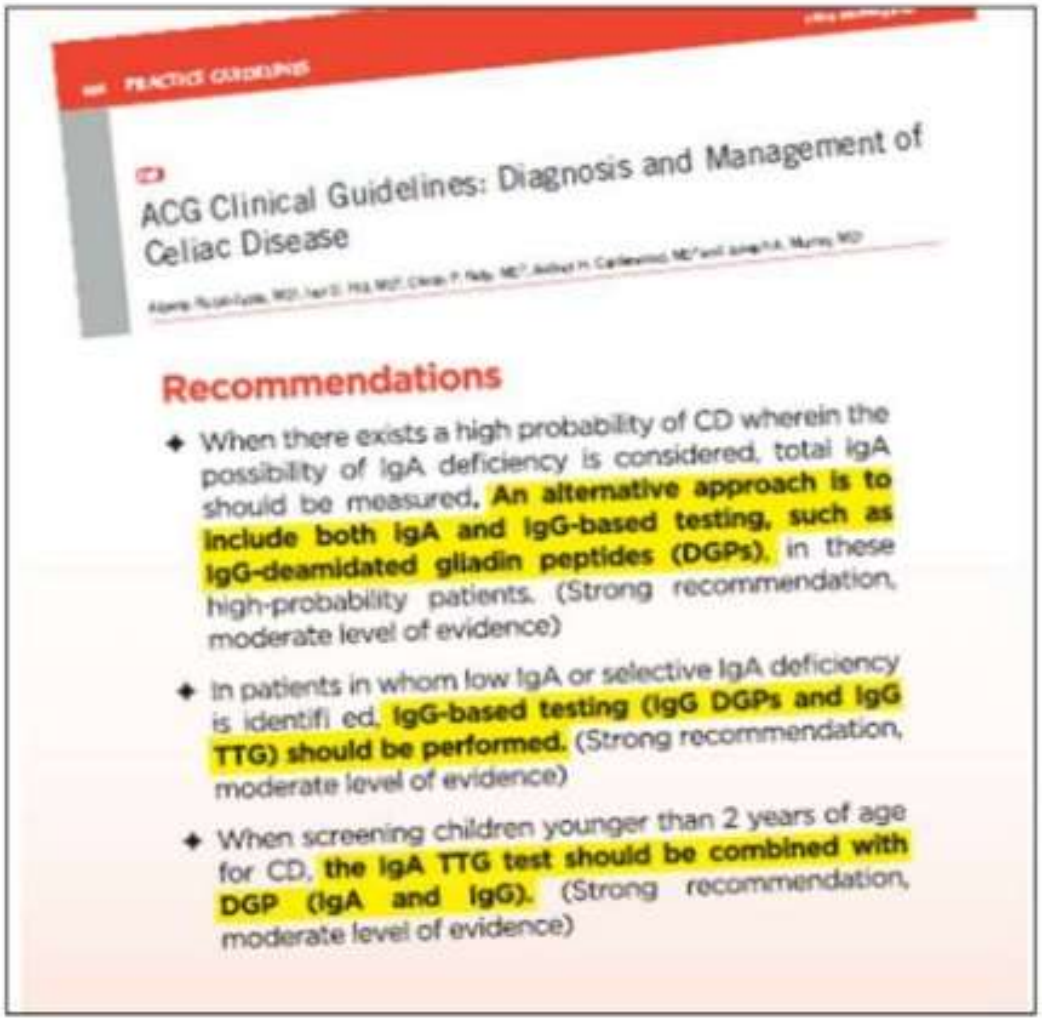
Test	sensitivity	specificity
HLA-DQ2	94%	73%
HLA-DQ8	12%	81%

Serology Tests

Kind	subscription
Anti-tissue transglutaminase antibody (tTG – IgA and IgG)	most sensitive
Anti-endomysial antibody (EMA-IgA	highly specific marker
Anti-deaminated gliadin peptide (DGP – IgA and IgG)	(-) tTG or EMA OR IgA deficient
Anti-gliadin antibody (AgA – IgG and IgA)	used for children < 2 yr

TEST PERFORMANCE AND UTILITY

- • TTG and deamidated gliadin IgA - Best combination of sensitivity and specificity
- EMA IgA- Excellent specificity
- TTG and deamidated gliadin IgG- Most appropriate in context of IgA deficiency
- HLA-DQ2 and HLA-DQ8 - Useful as rule-out test



PRACTICE GUIDELINES

ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease

Recommendations

- When there exists a high probability of CD wherein the possibility of IgA deficiency is considered, total IgA should be measured. **An alternative approach is to include both IgA and IgG-based testing, such as IgG-deamidated gliadin peptides (DGPs),** in these high-probability patients. (Strong recommendation, moderate level of evidence)
- In patients in whom low IgA or selective IgA deficiency is identified, **IgG-based testing (IgG DGPs and IgG TTG) should be performed.** (Strong recommendation, moderate level of evidence)
- When screening children younger than 2 years of age for CD, **the IgA TTG test should be combined with DGP (IgA and IgG).** (Strong recommendation, moderate level of evidence)

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ORIGINAL ARTICLE

Celiac disease serology in patients with different pretest probabilities: Is biopsy avoidable?

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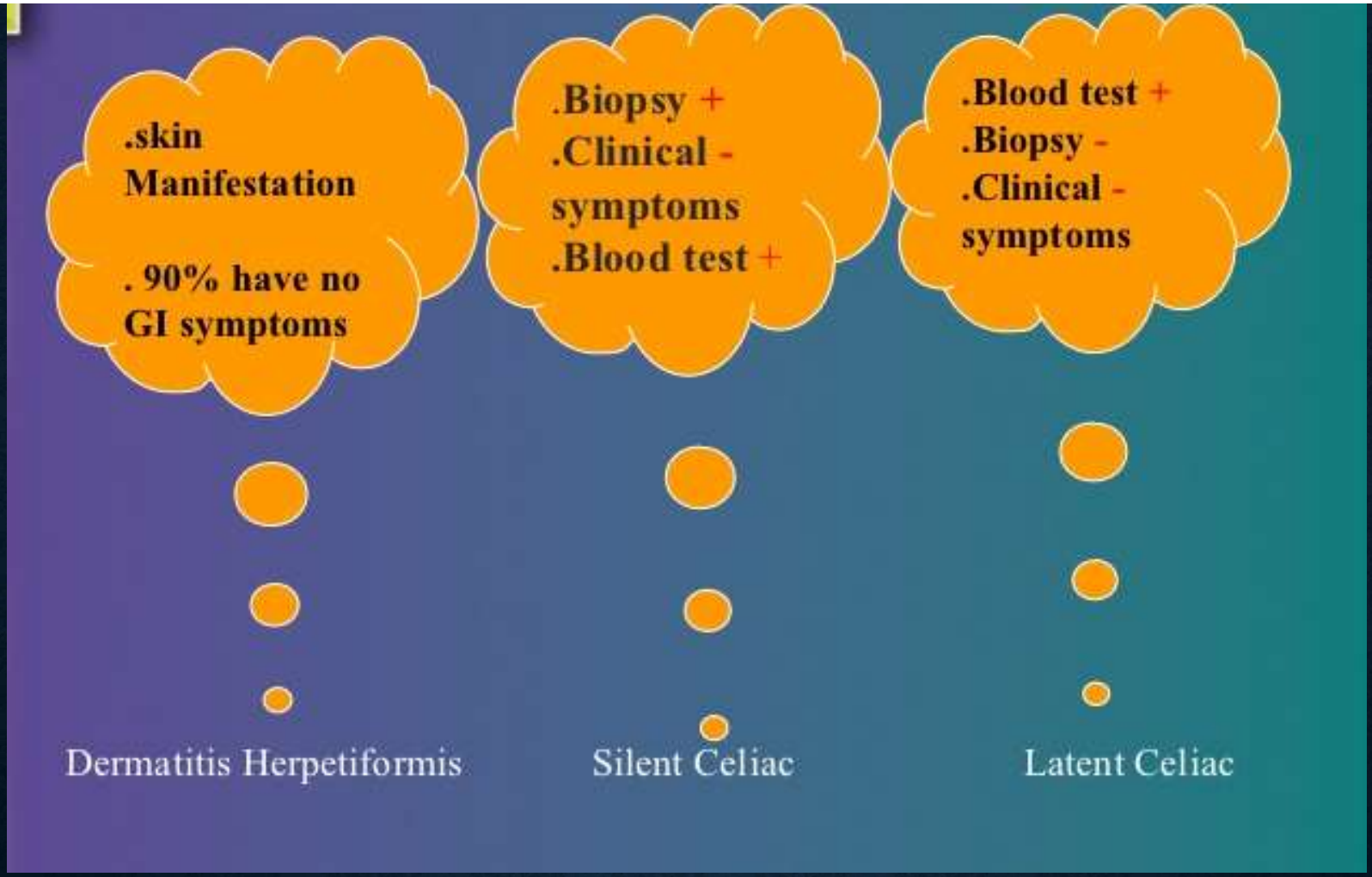
Abstract

AIM: To establish the diagnostic performance of sev-

CONCLUSION: The DGP/tTG Screen assay could be considered as the best initial test for CD. Combinations of two tests, including a DGP/tTG Screen, might be able to diagnose CD accurately in different clinical scenarios making biopsy avoidable in a high proportion of subjects.

Key words: Celiac disease; Serology; Gliadin peptide antibodies; Tissue transglutaminase; Antigliadin antibodies; Small bowel biopsy; Diagnostic accuracy

Peer reviewers: Chew Theam Soon, BMedSci, MBChB, MRCP, University of Manchester, 805 The Lock Building, 41 Whitworth


.skin
Manifestation
. 90% have no
GI symptoms
.Biopsy +
.Clinical -
symptoms
.Blood test +
.Blood test +
.Biopsy -
.Clinical -
symptoms
Dermatitis Herpetiformis
Silent Celiac
Latent Celiac

AIMS OF MANAGEMENT

- Correct existing deficiencies of iron, folate and /or vitamin-D
- Achieve mucosal healing through a lifelong gluten-free diet.
- Dietetic follow up is the key role of management.

THERAPEUTIC STRATEGIES

Detoxifying gluten before its ingestion

- Lactobacilli-based sourdough bread from Italy

Detoxifying gluten while in the stomach, before it reaches the small intestine Using enzymes to completely digest gluten

- From yeasts (Aspergillus Niger: AN-PEP)
- From bacteria (ALV-003)
- KumaMax

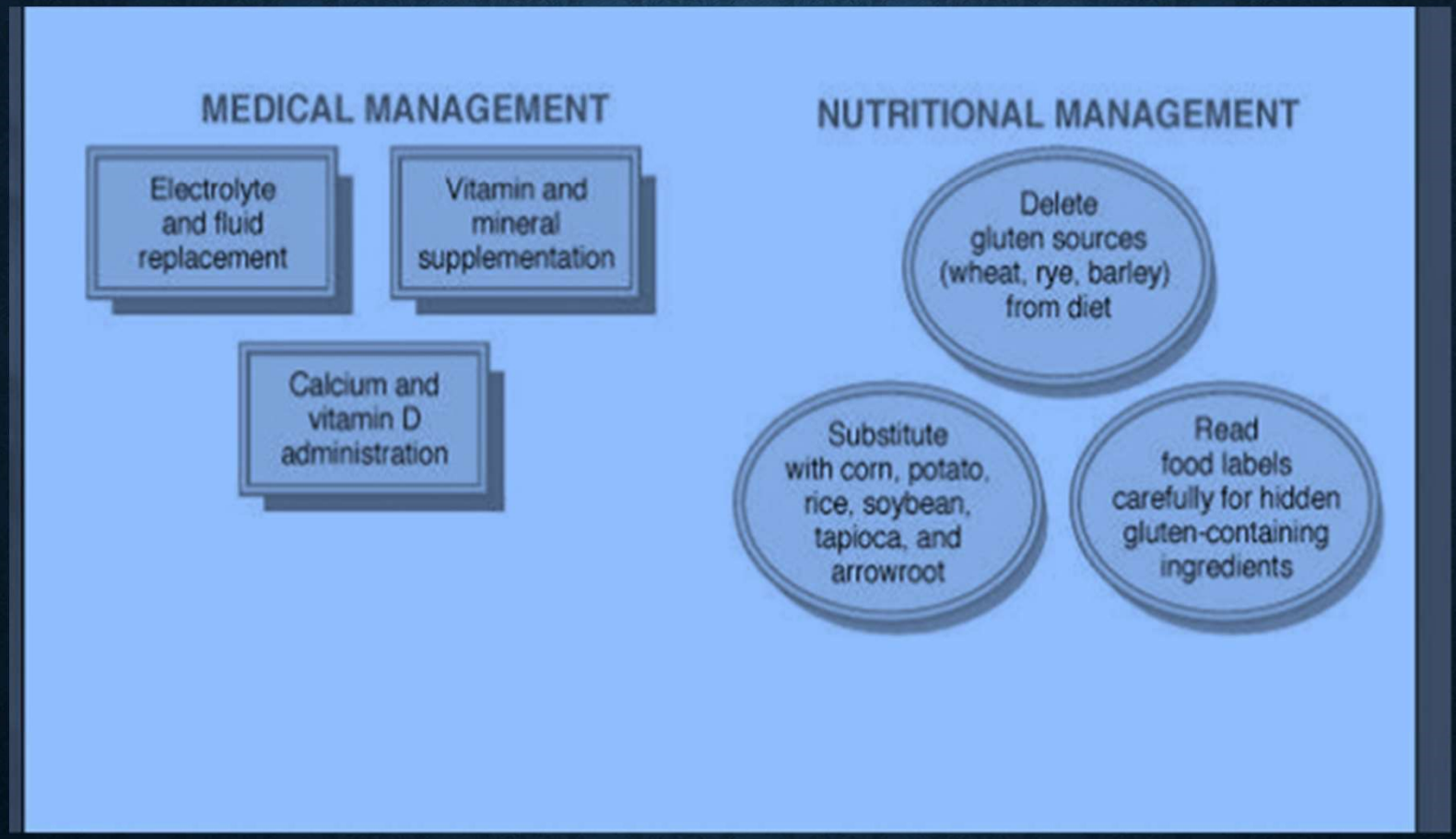
Blocking gluten passage across the lining of small intestine

- Anti-Zonulin (Lorazatide)

Developing a “therapeutic vaccine” to restore gluten tolerance, thus curing celiac disease

TREATMENT

- LIFELONG STRICT ADHERENCE TO A GLUTEN FREE DIET
- PRUDENT TO EXCLUDE OATS TO AS THERE MAYBE CONTAMINATION WITH GLUTEN DURING HARVESTING, MILLING, AND SHIPPING
- THE CODEX ALIMENTARIUS DEFINES GLUTEN FREE AS <20PPM
- THE THRESHOLD SHOULD BE SET FOR <50MG/DAY, ALTHOUGHT INDIVIDUAL VARIABILITY MAKES IT DIFFICULT TO SET A UNIVERSAL THRESHOLD
- MONITORING WITH PERIODIC VISITS FOR ASSESSMENT OF SYMPTOMS, GROWTH, PHYSICAL EXAMINATION AND ADHERENCE TO THE GLUTEN FREE DIET.


MEDICAL MANAGEMENT
Electrolyte and fluid replacement
Vitamin and mineral supplementation
Calcium and vitamin D administration
NUTRITIONAL MANAGEMENT
Delete gluten sources (wheat, rye, barley) from diet
Substitute with corn, potato, rice, soybean, tapioca, and arrowroot
Read food labels carefully for hidden gluten-containing ingredients

Treatment:

THE GLUTEN FREE DIET CAN BE LOW IN:

- High protein
- High calorie
- High Iron , folic acid, vit B12 , A, K, and D as water soluble B vitamins (thiamine, riboflavin, niacin, folate)
- Calcium
- Zinc
- Magnesium
- Fiber

- The only treatment is the lifelong adherence to the gluten-free diet.

- Gluten → small intestine start to heal
  → overall health improves

What Foods Contain Gluten?

jennifer's kitchen.com

Gluten is commonly found in bread and baked goods.

But gluten can also be hidden in the most unsuspecting places.


PHOTO ILLUSTRATION/GETTY IMAGES

Allowed Food	Avoid unless labeled Gluten Free	Avoid Food
Beans, seeds, nuts in their natural, unprocessed form	Beer	Barley (malt, malt flavoring and malt vinegar)
Fresh eggs	Breads, bread crumbs	Rye
Fresh meats, fish and poultry	Cakes, pies, cookies, crackers	Triticale (a cross between wheat and rye)
Fruits and vegetables	Candies	Wheat, bulgur
Most dairy products	Cereals	Seitan
Teff (tef)	Salad dressings, sauces including soy sauce	Durum flour
Amaranth	Croutons	Farina flour
Buckwheat	French fries	Graham flour
Corn (maize)	Gravies	Kamut
Millet	Imitation meat or seafood	Semolina
Quinoa	Matzo	Spelt
Rice	Pastas	Couscous
Sorghum	Processed luncheon meats	Triticale

Affordable Gluten Free Dinners

by Kimberlee Stokes

Healthy Foods That Are Naturally Gluten-Free

jennifer's kitchen.com

Vegetables

Legumes

Nuts and Seeds

Fruits

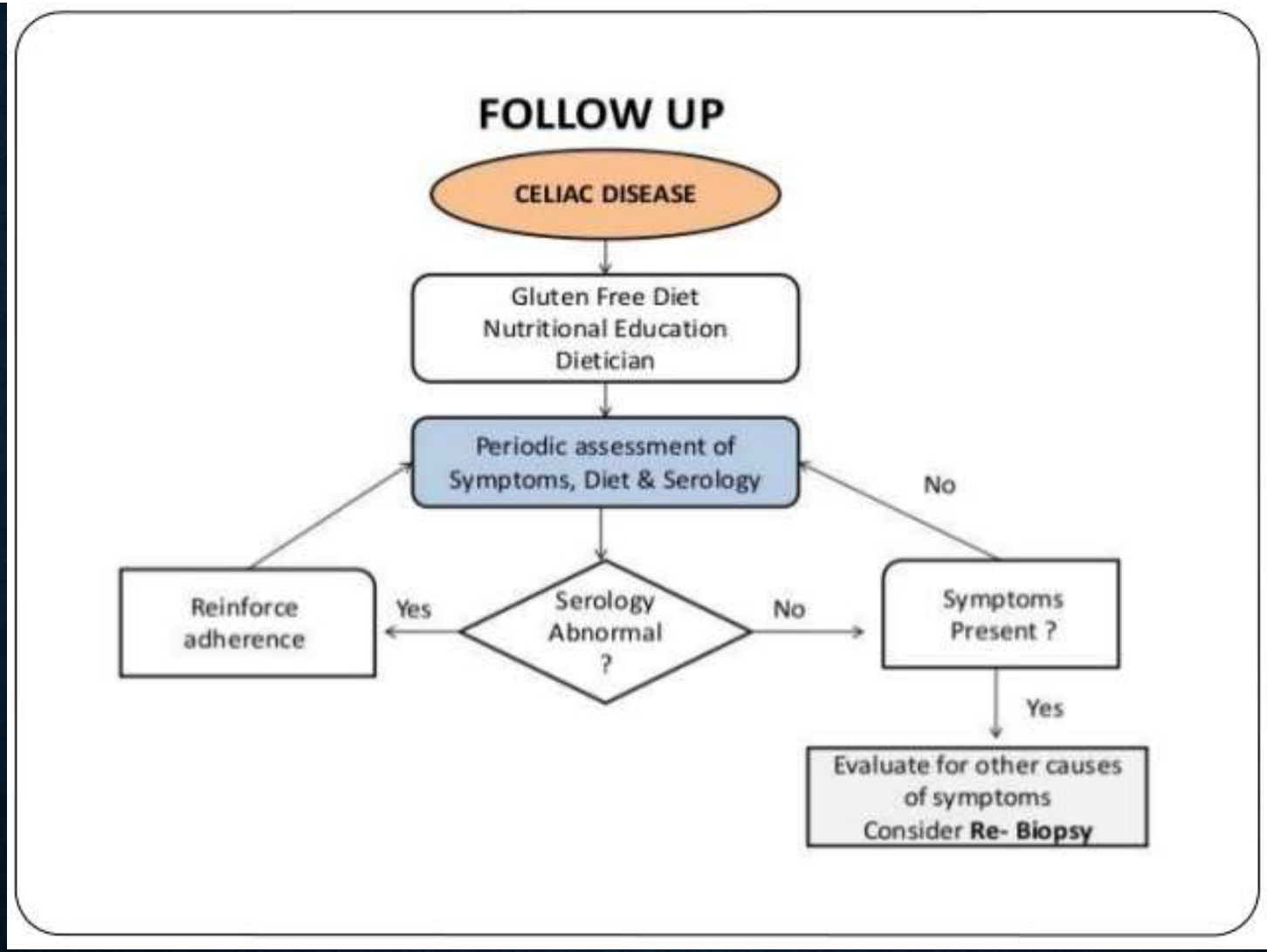
... including olives and avocados

Some Grains

... like buckwheat and quinoa

Experimental treatments

- Genetically engineered wheat species, or wheat species that have been selectively bred to be minimally immunogenic
- A combination of enzymes (prolyl endopeptidase and a barley glutamine-specific cysteine endopeptidase (EP-B2)) that degrade the putative 33-mer peptide in the duodenum. This combination would enable celiac disease patients to consume gluten-containing products

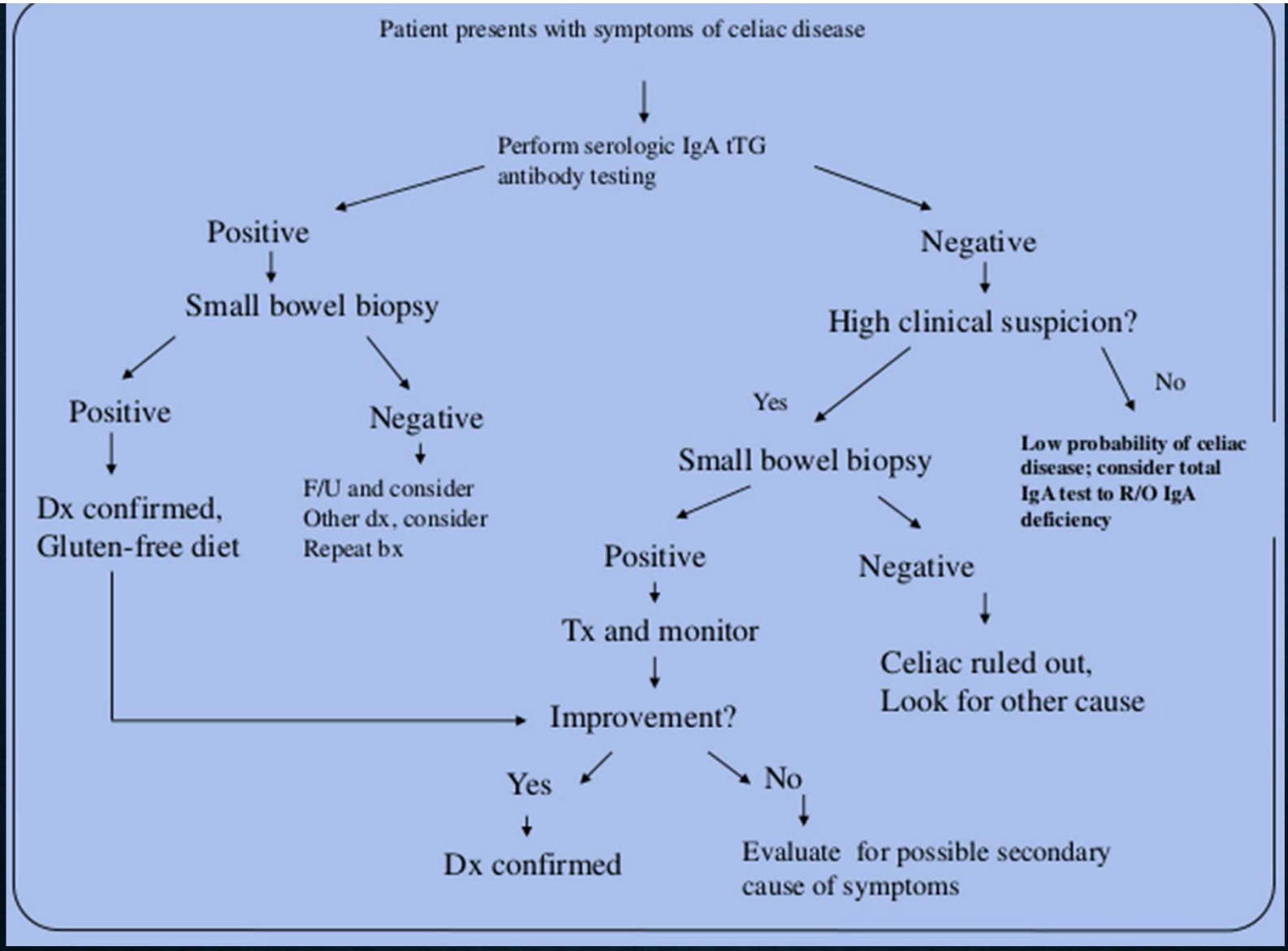

FOLLOW UP
CELIAC DISEASE
Gluten Free Diet
Nutritional Education
Dietician
Periodic assessment of
Symptoms, Diet & Serology
No
Reinforce
adherence
Yes
Serology
Abnormal
?
No
Symptoms
Present ?
Yes
Evaluate for other causes
of symptoms
Consider Re- Biopsy

FOLLOW UP

- SEROLOGICAL MARKERS ARE USED TO MONITOR COMPLIANCE WITH A GLUTEN FREE DIET.
- ANTIBODY LEVELS RETURN TO NORMAL WITHIN 3-12 MONTHS OF STARTING A GLUTEN-FREE DIET BUT MAY TAKE UPTO 30 MONTHS IF THE TITERS ARE HIGH.
- A REPEAT SMALL BOWEL BIOPSY AFTER 3-4 MONTHS OF STARTING A GLUTEN FREE DIET IS NOT NECESSARY IF THE PATIENT IS RESPONDING WELL TO THERAPY.
- IF THE PATIENT DOES NOT RESPOND AS EXPECTED DESPITE ADHERENCE TO A GLUTEN-FREE DIET, THE PHYSICIAL SHOULD CONSIDER OTHER DISEASES THAT MIMIC CELIAC DISEASE.

COMPLICATIONS

- Intestinal T-cell lymphoma
- Carcinoma of small intestine
- Ulcerative jejunitis
- Complications of nutritional deficiency
  - Anemia
  - Osteoporosis
  - Osteomalacia
  - Peripheral neuropathy


Patient presents with symptoms of celiac disease
Perform serologic IgA tTG antibody testing
Positive
Small bowel biopsy
Positive
Dx confirmed, Gluten-free diet
Negative
F/U and consider Other dx, consider Repeat bx
Negative
High clinical suspicion?
Yes
Small bowel biopsy
Positive
Tx and monitor
Improvement?
Yes
Dx confirmed
No
Evaluate for possible secondary cause of symptoms
Negative
Celiac ruled out, Look for other cause
No
Low probability of celiac disease; consider total IgA test to R/O IgA deficiency

Refractory Disease

This may be because

- The disease has been present for so long that the intestines are no longer able to heal on diet alone
- The patient is not adhering to the diet
- Because the patient is consuming foods that are inadvertently contaminated with gluten
- In this case steroids and immunosuppresents should be considered

NEW APPROACHES

WITH IMPROVING INSIGHT INTO THE PATHOGENESIS OF CELIAC DISEASE, SEVERAL POSSIBLE DRUG TARGETS HAVE BEEN SUGGESTED.

- The new strategies include degradation of gluten intraluminally
- Reduction of mucosal permeability
- Inhibition of the transglutaminase 2 enzyme
- Blocking antigen presentation by HLA-DQ2 or HLA-DQ8 modulation of the immune responses of many cytokines and vaccination.
- Non-dietary treatment options are warranted either as adjunctive therapy together with dieting or to replace the gluten-free diet.

While the gluten-free diet is still the only treatment for CD, recent investigations have explored alternative approaches, including the use of

- Altered nonimmunogenic wheat variants
- Enzymatic degradation of gluten
- Tissue transglutaminase inhibitors
- Induction of tolerance and Peptides to restore integrity to intestinal tight junctions.

The identification of alternative or complementary treatments to the gluten-free diet brings hope for patients unavoidably burdened by diet restrictions.

Thanks For listening: