

# Definition

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**Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals.**

**It occurs in symptomatic subjects with gastrointestinal and non-gastrointestinal symptoms, and in some asymptomatic individuals, including subjects :**  
**With certain genetic associations**  
**Certain autoimmune disorders.**

# Expanded Definition

- **Celiac disease is an autoimmune condition**
- **Occurs in genetically susceptible individuals**
  - DQ2 and/or DQ8 positive HLA haplotype is necessary but not sufficient
- **A *unique* autoimmune disorder because:**
  - both the environmental trigger (gluten) and the autoantigen (tissue Transglutaminase) are known
  - elimination of the environmental trigger leads to a complete resolution of the disease

# Clinical Manifestations

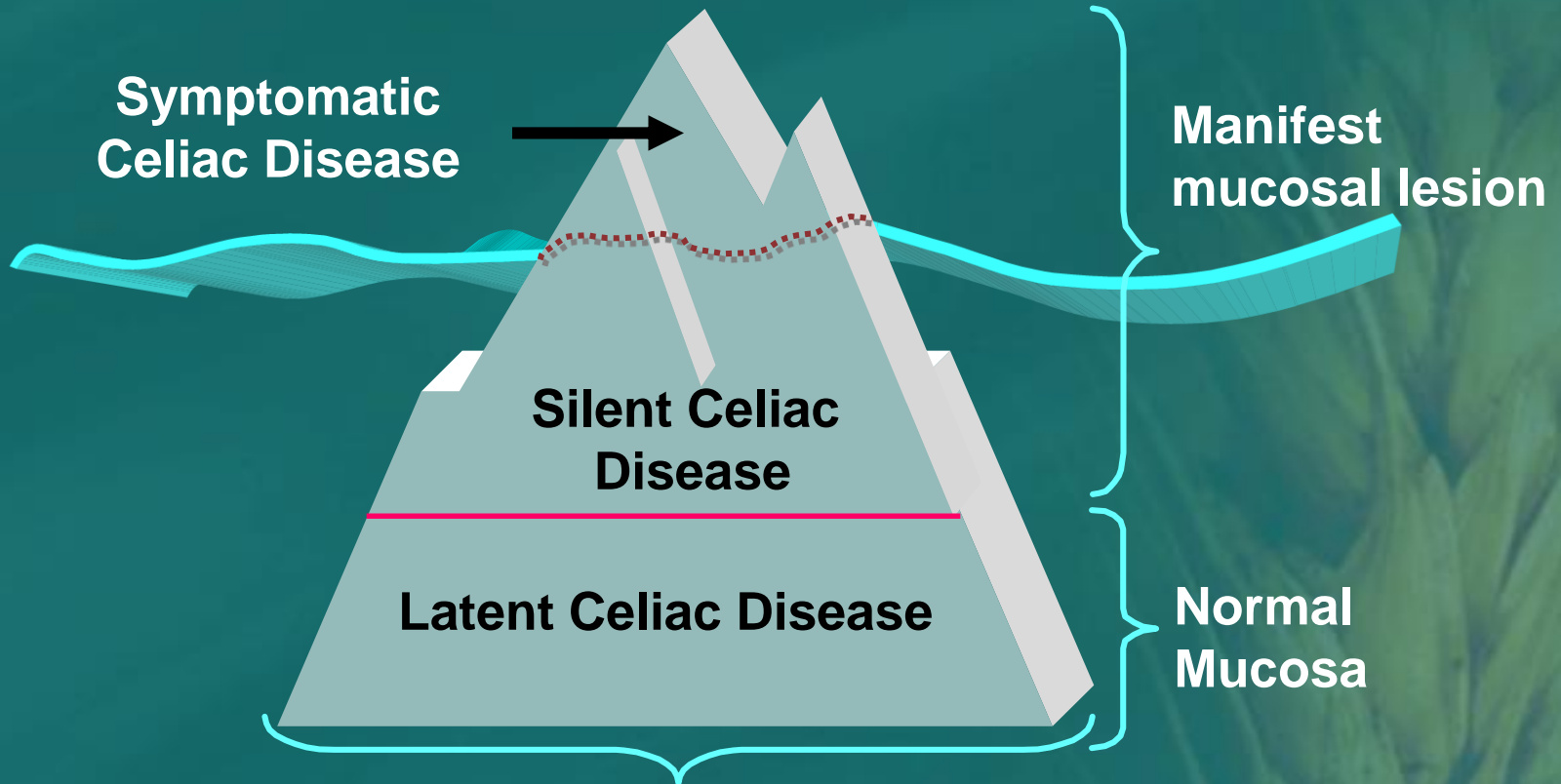
# Clinical Manifestations

- Gastrointestinal (“*classical*”)
- Non-gastrointestinal ( “*atypical*”)
- Asymptomatic

*In addition, Celiac Disease may be associated with other conditions, and mostly with:*

- Autoimmune disorders
- Some syndromes

# The Celiac Iceberg



Genetic susceptibility: - DQ2, DQ8  
Positive serology

# Gastrointestinal Manifestations ("Classic")

Most common age of presentation: 6-24 months

- Chronic or recurrent diarrhea
- Abdominal distension
- Anorexia
- Failure to thrive or weight loss
- Abdominal pain
- Vomiting
- Constipation
- Irritability

*Rarely: Celiac crisis*

# Typical Celiac Disease





# Non Gastrointestinal Manifestations

Most common age of presentation: older child to adult

- Dermatitis Herpetiformis
- Dental enamel hypoplasia of permanent teeth
- Osteopenia/Osteoporosis
- Short Stature
- Delayed Puberty
- Iron-deficient anemia resistant to oral Fe
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications

# Dermatitis Herpetiformis



- Erythematous macule > urticarial papule > tense vesicles
- Severe pruritus
- Symmetric distribution
- 90% no GI symptoms
- 75% villous atrophy
- Gluten sensitive

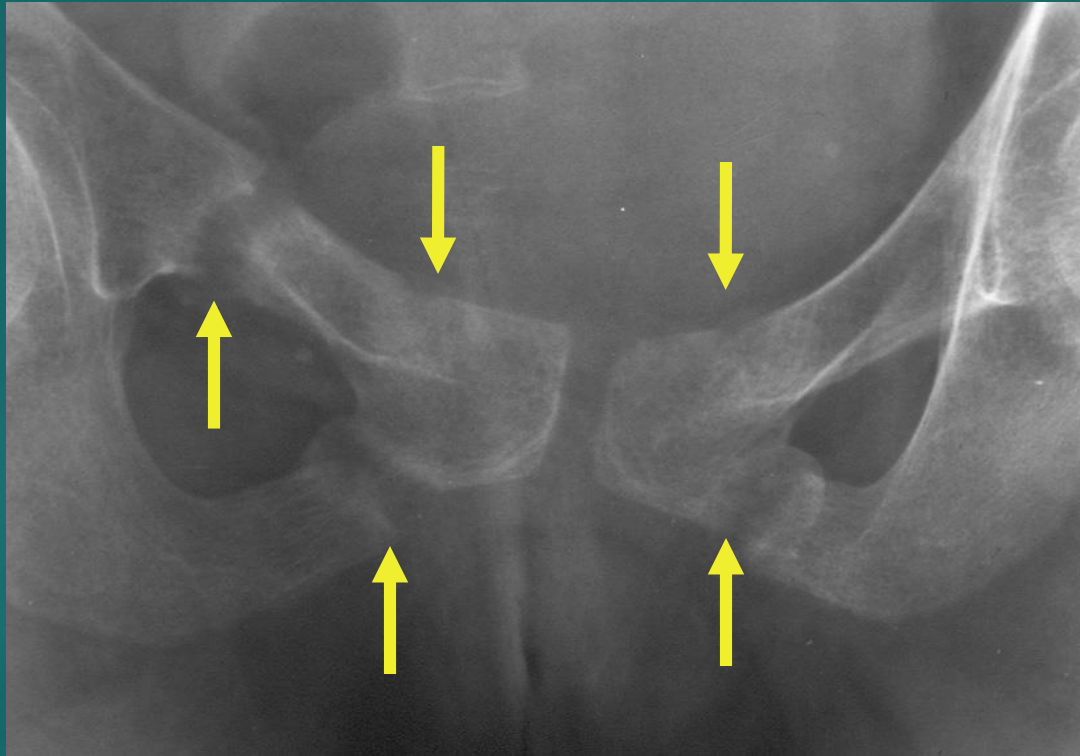
Garioch JJ, et al. *Br J Dermatol.* 1994;131:822-6.  
Fry L. *Baillieres Clin Gastroenterol.* 1995;9:371-93.  
Reunala T, et al. *Br J Dermatol.* 1997;136:315-8.

# Dental Enamel Defects



*Involve the secondary dentition  
May be the only presenting sign of Celiac Disease*

# Osteoporosis



*Low bone mineral density improves in children on a gluten-free diet.*

# Short Stature/Delayed Puberty

- **Short stature in children / teens:**
  - • ~10% of short children and teens have evidence of celiac disease
- **Delayed menarche:**
  - Higher prevalence in teens with untreated Celiac Disease

# Fe-Deficient Anemia Resistant to Oral Fe

- Most common non-GI manifestation in some adult studies
- 5-8% of adults with unexplained iron deficiency anemia have Celiac Disease
- In children with newly diagnosed Celiac Disease:
  - Anemia is common
  - Little evidence that Celiac Disease is common in children presenting with anemia

# Hepatitis

- **Some evidence for elevated serum transaminases (ALT, AST) in adults with untreated Celiac Disease**
  - **Up to 9% of adults with elevated ALT, AST may have silent Celiac Disease**
  - **Liver biopsies in these patients showed non-specific reactive hepatitis**
  - **Liver enzymes normalized on gluten-free diet**

# Arthritis and Neurological Problems

- **Arthritis in adults**
  - Fairly common, including those on gluten-free diets
- **Juvenile chronic arthritis**
  - Up to 3% have Celiac Disease
- **Neurological problems**
  - Epilepsy with cranial calcifications in adults
  - Evidence for this condition in children with Celiac Disease is not as strong



# 3 – Asymptomatic

**Silent**

**Latent**

- **Silent:**  
*No or minimal symptoms, “damaged” mucosa and positive serology*

**Identified by screening asymptomatic individuals from groups at risk such:**

- First degree relatives
- Down syndrome patients
- Type 1 diabetes patients, etc.

# 3 – Asymptomatic

Silent

Latent

- Latent: *No symptoms, normal mucosa*
  - May show positive serology. Identified by following in time asymptomatic individuals previously identified at screening from groups at risk. These individuals, given the “right” circumstances, will develop at some point in time mucosal changes ( $\pm$  symptoms), although it may be even decades later.

# Asymptomatic

- Asymptomatic patients are still at risk of osteopenia/osteoporosis
- Treatment with a gluten-free diet is recommended for asymptomatic children with proven intestinal changes of Celiac Disease who have:
  - type 1 diabetes
  - selective IgA deficiency
  - Down syndrome
  - Turner syndrome
  - Williams syndrome
  - autoimmune thyroiditis
  - a first degree relative with Celiac Disease

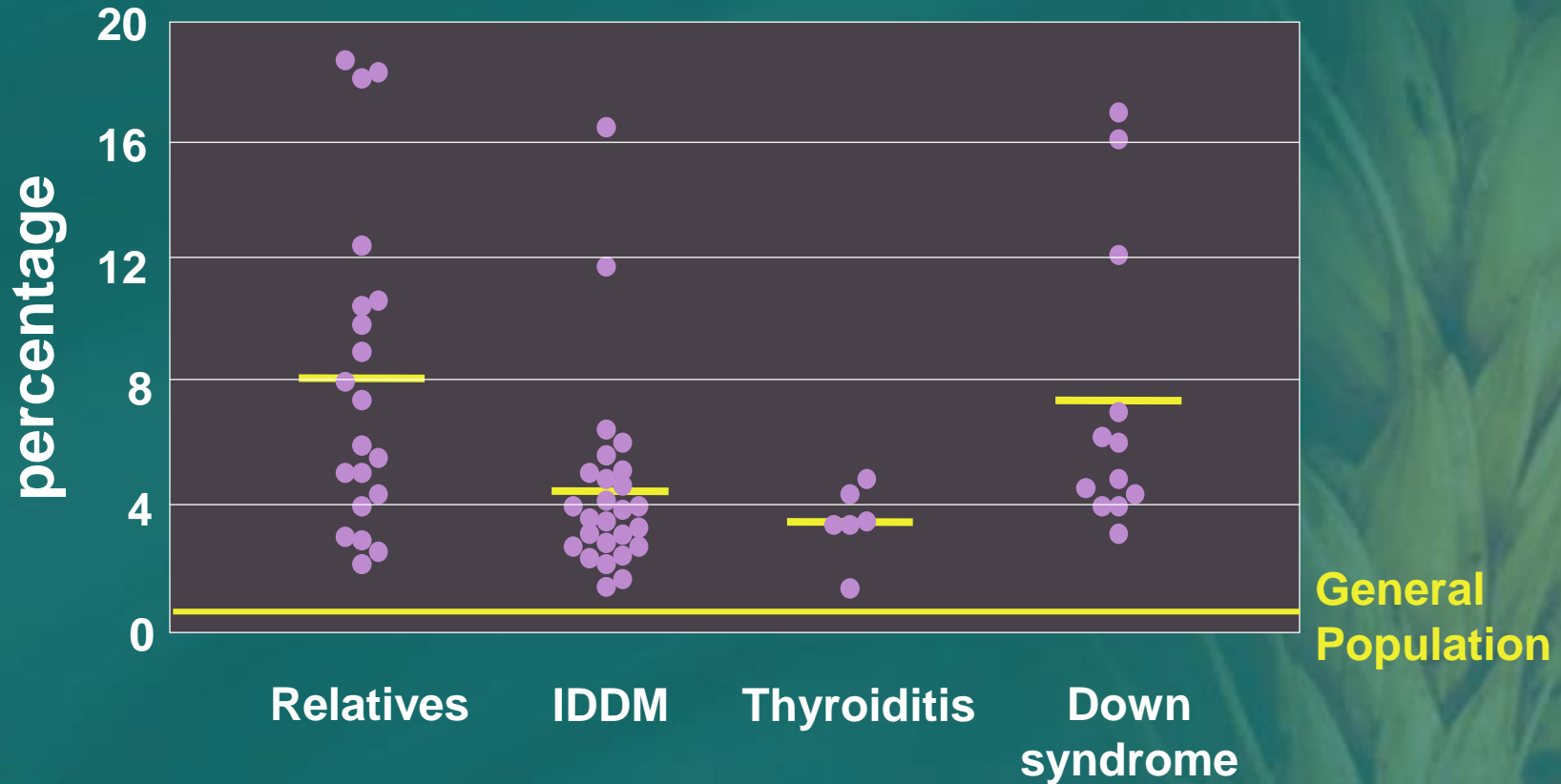
# Associated Conditions

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The prevalence of Celiac Disease is higher in patients who have the following:

- Certain genetic disorders or syndromes
- Other autoimmune conditions
- Relative of a biopsy-proven celiac

# Associated Conditions



# Genetic Disorders

- Down Syndrome: 4-19%
- Turner Syndrome: 4-8%
- Williams Syndrome: 8.2%
- IgA Deficiency: 7%
  - Can complicate serologic screening

# Prevalence of Celiac Disease is Higher in Other Autoimmune Conditions

Type 1 Diabetes Mellitus:	3.5 - 10%
Thyroiditis:	4 - 8%
Arthritis:	1.5 - 7.5%
Autoimmune liver diseases:	6 - 8%
Sjögren's syndrome:	2 - 15%
Idiopathic dilated cardiomyopathy:	5.7%
IgA nephropathy:	3.6%



# Relatives

- **Healthy population:** 1:133 ( 0.75% )
- **1st degree relatives:** 1:10 to 1:22
- **2nd degree relatives:** 1:24 to 1:39

# Celiac Disease and Autoimmunity

- Prevalence of autoimmune disorders in celiac disease related to duration of gluten exposure
  - Diagnosed before 2 years of age: 5%
  - Age 2-10 years: 17%
  - Greater than age 10 years: 24%
- Increased incidence of autoimmune disease in patients with IDDM and 'silent' Celiac Disease and their first degree relatives who were EMA+

# Complications

# Major Complications of Celiac Disease

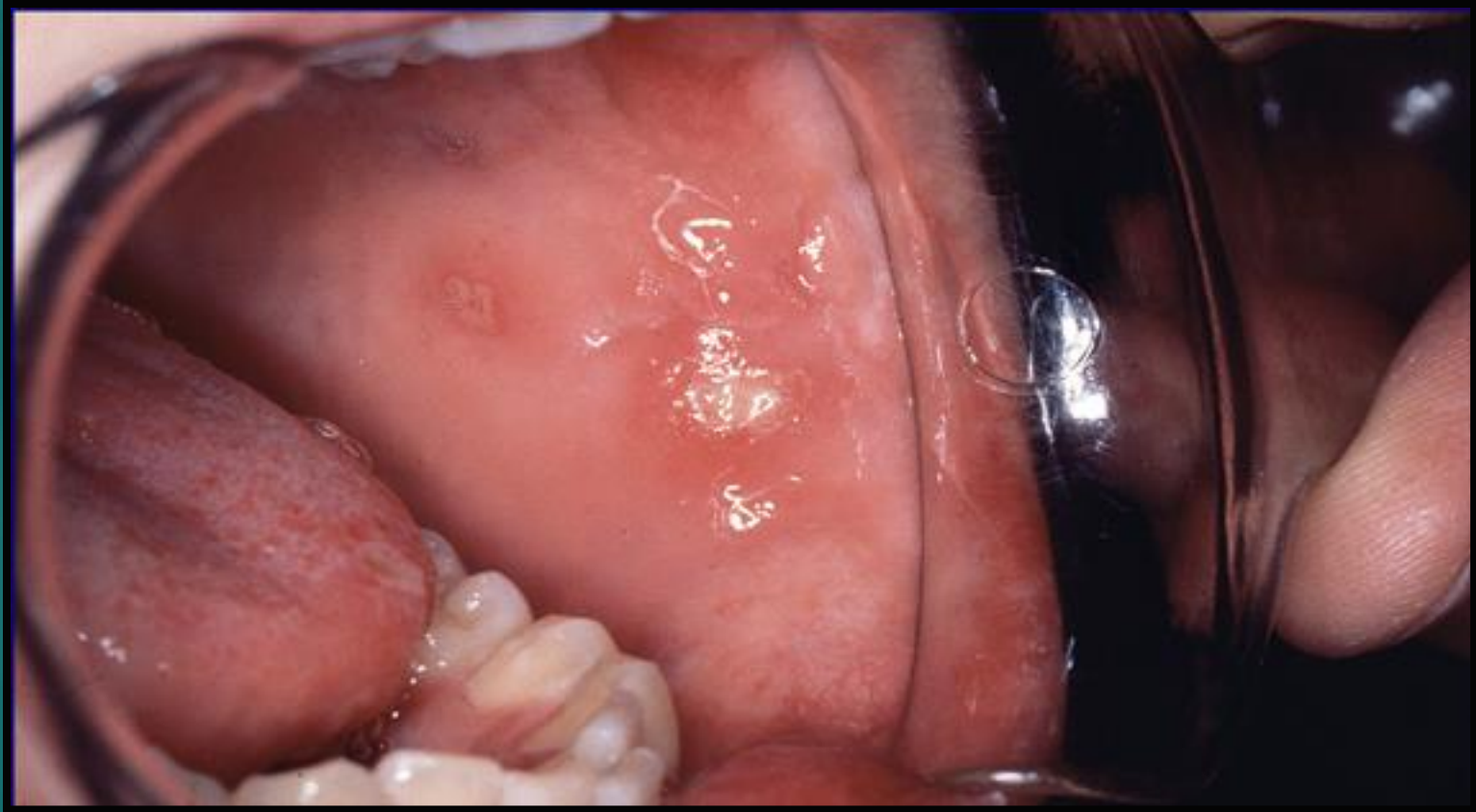
- Short stature
- Dermatitis herpetiformis
- Dental enamel hypoplasia
- Recurrent stomatitis
- Fertility problems
- Osteoporosis
- Gluten ataxia and other neurological disturbances
- Refractory celiac disease and related disorders
- Intestinal lymphoma

# Celiac Disease

## Associated Disorders

- Autoimmune diseases: type 1 diabetes, Hashimoto's thyroiditis, autoimmune hepatitis, adrenal failure
- Down syndrome
- IgA deficiency
- Turner syndrome
- Williams syndrome

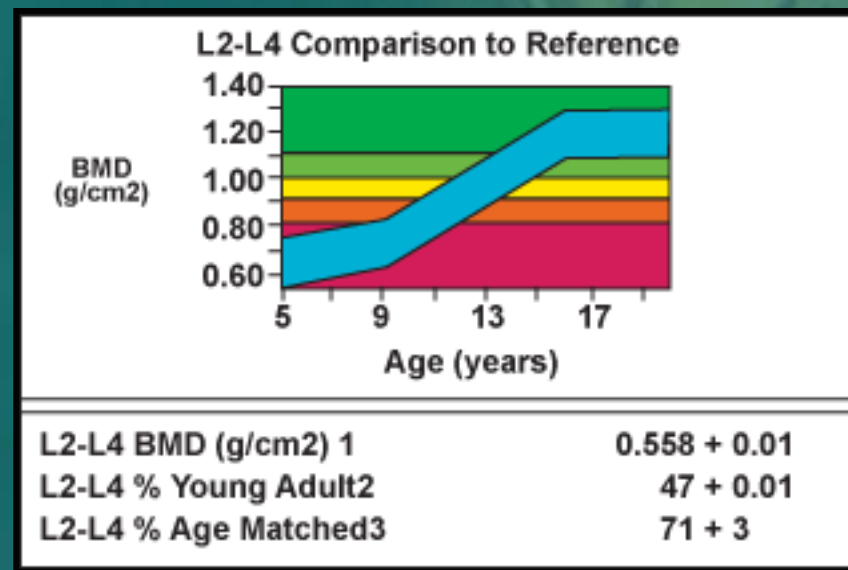
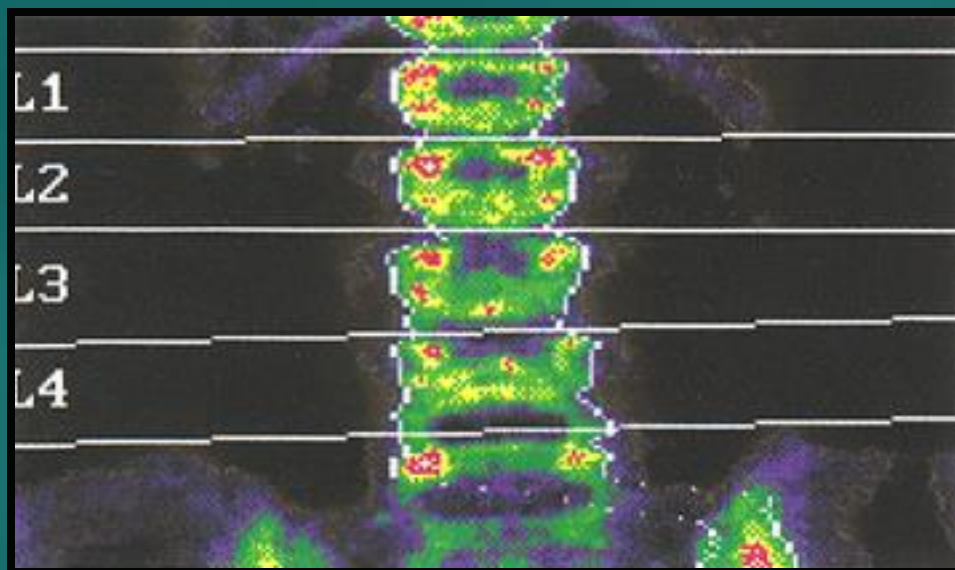
# Recurrent Aphthous Stomatitis



# Dermatitis Herpetiformis

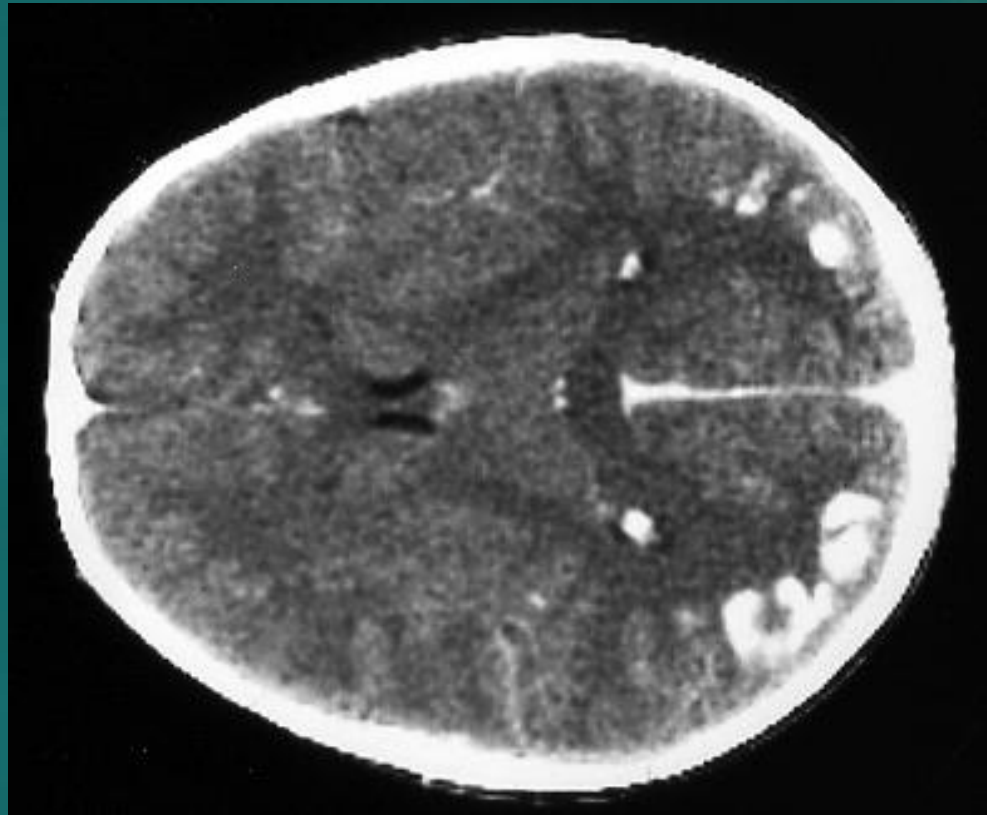


# Low Bone Mineral Density (DXA) in a Child With Untreated Celiac Disease





# CT Scan Showing Occipital Calcifications in a Boy with Celiac Disease and Epilepsy



# Celiac Disease Complicated by Enteropathy-Associated T-cell Lymphoma (EATL)



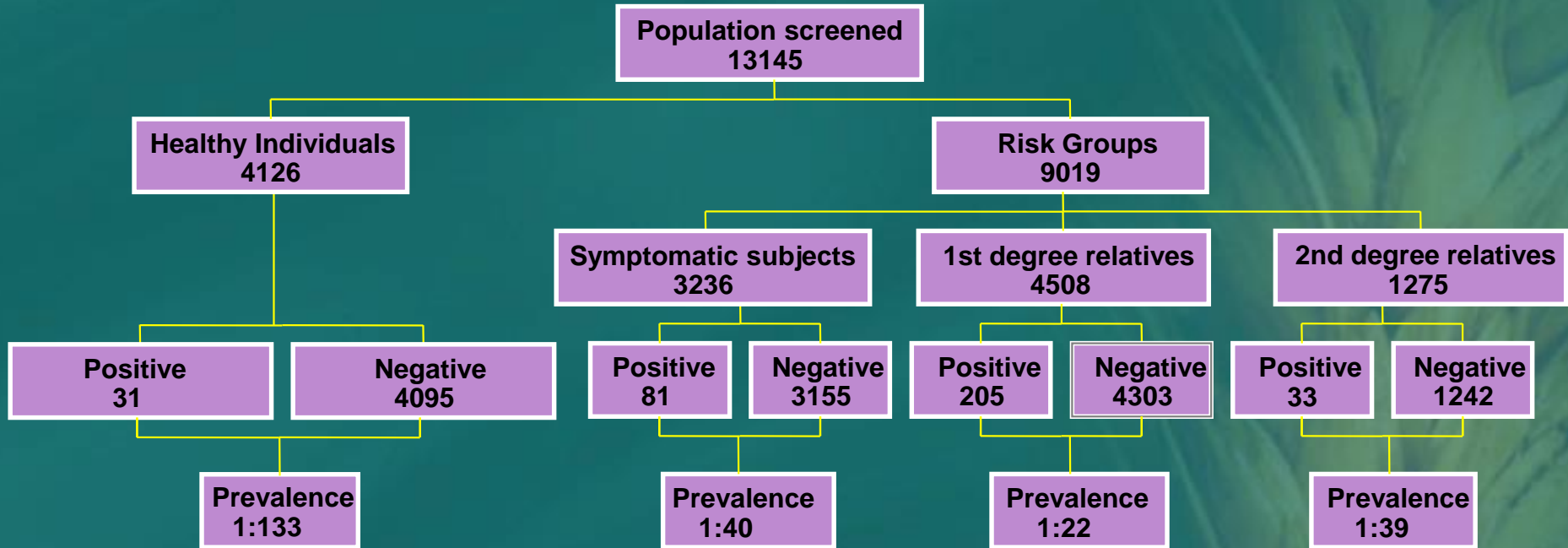
# Epidemiology

# The Changing Celiac Epidemiology

The availability of sensitive serological markers made it possible to discover Celiac Disease even when the clinical suspicion was low.

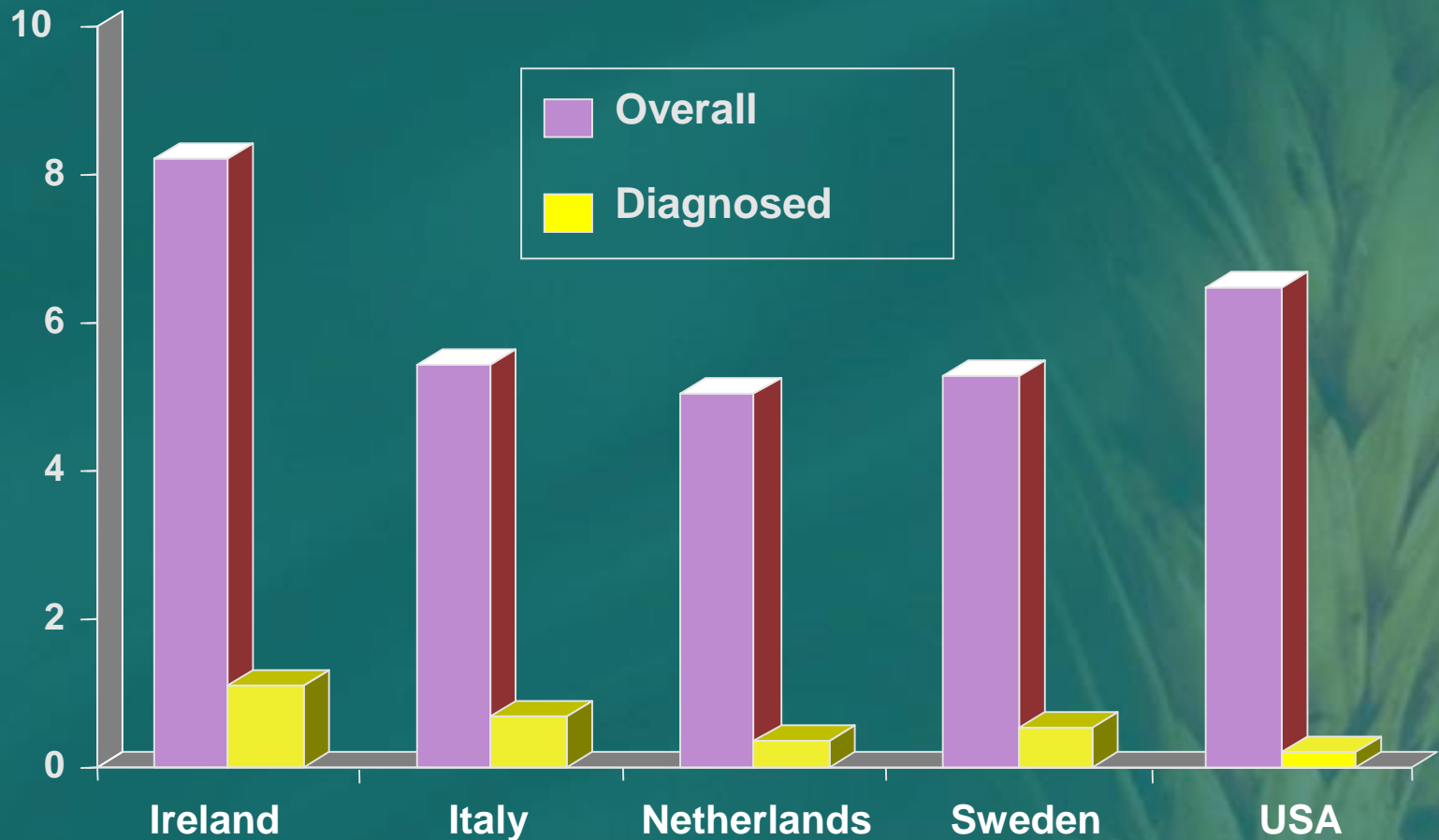


# Celiac Disease Epidemiological Study in USA



Projected number of celiacs in the U.S.A.: **2,115,954**  
 Actual number of known celiacs in the U.S.A.: **40,000**  
 For each known celiac there are 53 undiagnosed patients.

# Celiac Disease Icebergs



# Increased Overall Mortality In Adult Life



AUTOIMMUNE DISEASES

OSTEOPOROSIS

LIVER DISEASES

CANCER

## ORIGINAL INVESTIGATION

### Causes of Death in Patients With Celiac Disease in a Population-Based Swedish Cohort

*Ulrika Peters, PhD, MPH; Johan Askling, MD; Gloria Gridley, MS; Anders Ekblom, MD, PhD; Martha Lincet, MD*

### Mortality in patients with coeliac disease and their relatives: a cohort study

*Giovanni Corrao, Gino Roberto Corazza, Vincenzo Bagheri, Giovanna Brusco, Carolina Ciacci, Mario Cottone, Carla Sategna Guldetti, Paolo Usai, Pietro Cesari, Maria Antonietta Pellì, Silvano Loperfido, Umberto Volta, Antonino Calabró, Maria Certo, for the Club del Tenue Study Group*

# Pathogenesis



# Pathogenesis



- Genetic predisposition
- Environmental triggers
  - Dietary
  - Non dietary?





# Genetics

- **Strong HLA association**
- **90 - 95% of patients HLA-DQ2 – also found in 20 - 30% of controls**
  - **Most of the remainder are HLA - DQ8**
- **10% of patients have an affected first degree relative**



# Genetics

- Concordance in monozygotic twins is 70%
- Concordance in HLA-identical siblings 30 - 40%, suggesting other genes or factors are involved



# Dietary Factors

**Gluten is a protein that contains the sub proteins gliadin and glutenin.**

**It is found in wheat, rye, barley and triticale ( a wheat-rye hybrid ).**

**No specific peptide has been found that activates disease in all Celiac Disease patients.**



# Non Dietary Factors

- Infections
  - Viral infections
    - sequence homology between  $\alpha$ -gliadin & adenovirus type 12 & 7, rubella and human herpesvirus 1
  - Parasitic infestations
    - sequence homology between  $\alpha$ -gliadin & *Plasmodium yoelli*
  - Other ?

# Tissue Transglutaminase (TTG)

- Normal gut enzyme released during injury and stabilizes the cross-linking of proteins in granulation tissue, thereby reducing proteolysis.
- Deamidates gliadin
  - In Celiac Disease: Autoantibodies against TTG correlate with active Celiac Disease and seem to be involved in pathogenesis of the disease.

# Diagnosis

# Diagnosis



## Diagnostic principles

- **Confirm diagnosis before treating**
  - **Diagnosis of Celiac Disease mandates a strict gluten-free diet for life**
    - following the diet is not easy
    - QOL implications
- **Failure to treat has potential long term adverse health consequences**
  - increased morbidity and mortality



# Serological Tests

- Deamidated gliadin antibodies (dAGA)
- Antiendomysial antibodies (EMA)
- Anti tissue transglutaminase antibodies (TTG)
  - first generation (guinea pig protein)
  - second generation (human recombinant)
- HLA typing

# Deamidated gliadin Antibodies

- Antibodies (IgG and IgA) to the gluten protein in wheat, rye and barley
- Advantages
  - relatively cheap & easy to perform
- Disadvantages
  - suboptimal sensitivity and specificity

# Endomysial Antibody - EMA

- IgA based antibody against reticulin connective tissue around smooth muscle fibers
- Advantages
  - high sensitivity and specificity
- Disadvantages
  - false negative in young children
  - operator dependent
  - expensive & time consuming
  - false negative in IgA deficiency

# Tissue Transglutaminase - TTG

- IgA based antibody against tissue transglutaminase (Celiac Disease autoantigen)
- Advantages
  - high sensitivity and specificity (human TTG)
  - non operator dependent (ELISA/RIA)
  - relatively cheap
- Disadvantages
  - false negative in young children
  - false negative in IgA deficiency
  - possibly less specific than EMA

# Serological Test Comparison

	Sensitivity %	Specificity %
AGA-IgG	69 – 85	73 – 90
AGA-IgA	75 – 90	82 – 95
EMA (IgA)	85 – 98	97 – 100
TTG (IgA)	90 – 98	94 – 97

# Serum IgA Level

- Individuals with IgA deficiency are at increased risk for Celiac Disease
- IgA deficient individuals will have negative EMA-IgA & TTG-IgA
- Check IgA levels with Celiac Disease serology in all symptomatic individuals
- Consider IgG based tests (EMA-IgG & TTG-IgG) in IgA deficiency

# HLA Tests

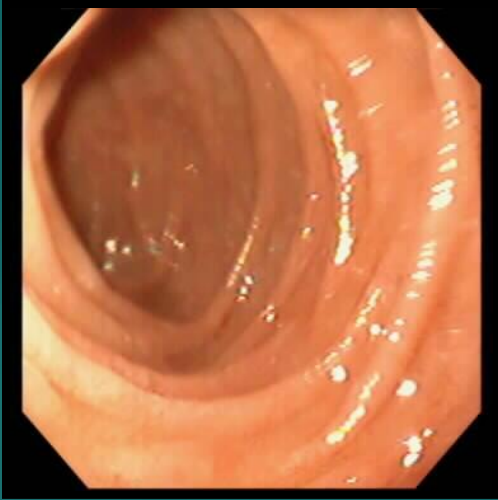
## HLA alleles associated with Celiac Disease

- DQ2 found in 90% of celiac patients
- DQ8 found in remaining patients
- DQ2 found in ~25-30% of general population

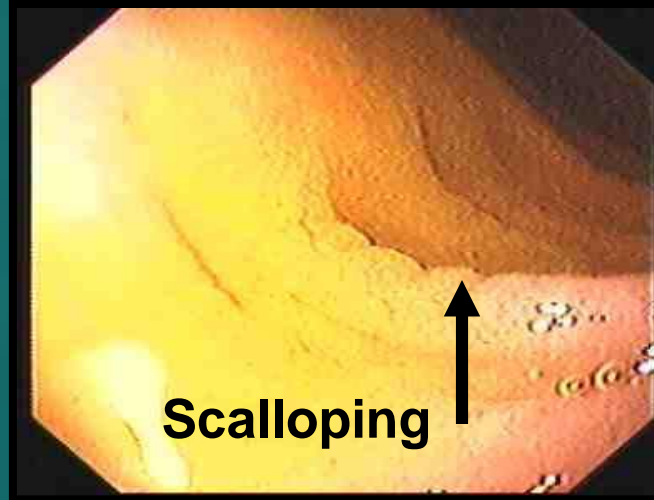
## Value of HLA testing

- High negative predictive value
  - Negativity for DQ2/DQ8 excludes diagnosis of Celiac Disease with 99% confidence

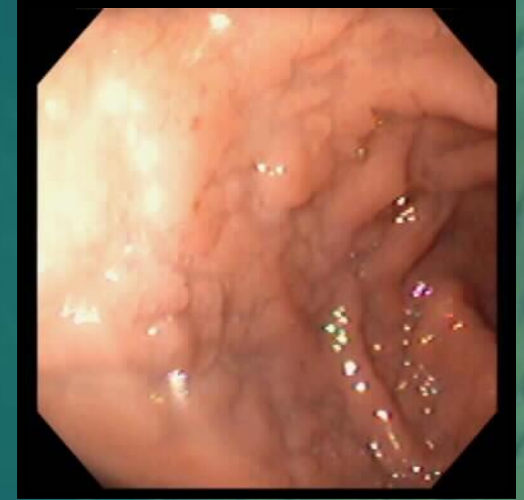
# Endoscopic Findings



Normal Appearing



Scalloping

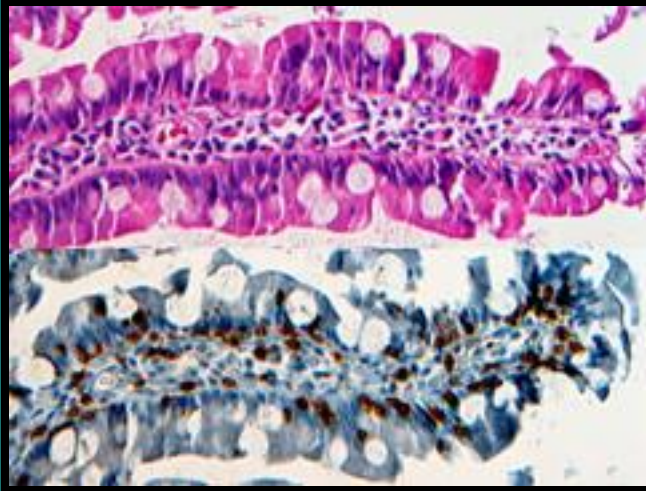


Nodularity



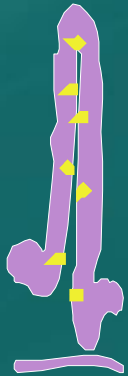
# Biopsy Diagnosis

- Histologic Features:
  - Increased IEL's ( > 30/100 enterocytes)
  - Loss of nuclear polarity
  - Change from columnar to cuboid
  - Lamina propria cellular infiltrate
  - Crypt elongation and hyperplasia
  - Increased crypt mitotic index
  - Progressive villous flattening



# Patterns of Mucosal Immunopathology

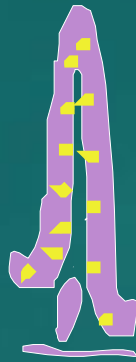
## Type 0



### Normal

Celiac Disease  
(latent)

## Type 1



### Infiltrative

Celiac  
Giardiasis  
Milk intolerance  
Tropical sprue  
Marasmus  
GVHR

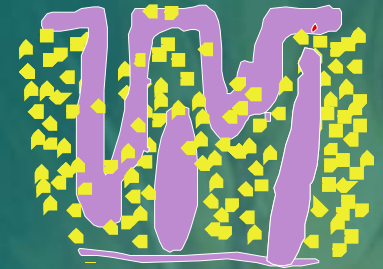
## Type 2



### Hyper plastic

Celiac  
Giardiasis  
Milk intolerance  
Tropical sprue  
Marasmus  
GVHR

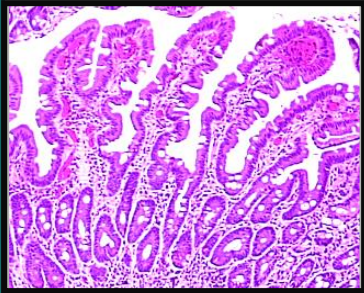
## Type 3



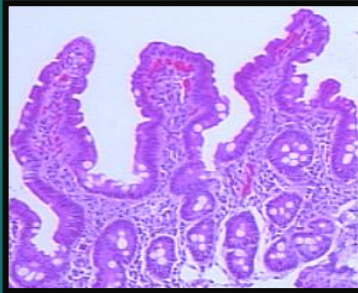
### Flat destructive

Celiac  
Giardiasis  
Milk intolerance  
Tropical sprue  
Marasmus  
GVHR

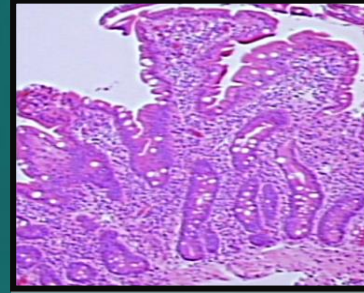
# Histological Features



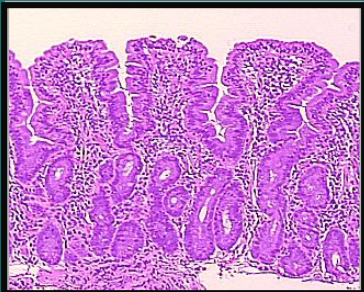
Normal 0



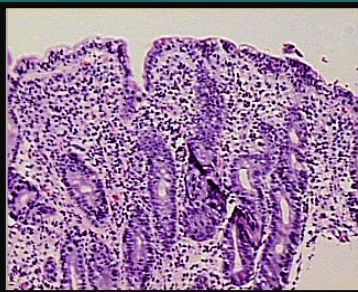
Infiltrative 1



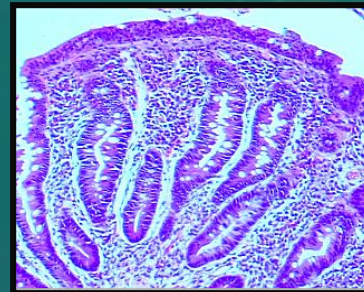
Hyperplastic 2



Partial atrophy 3a



Subtotal atrophy 3b



Total atrophy 3c

# Treatment