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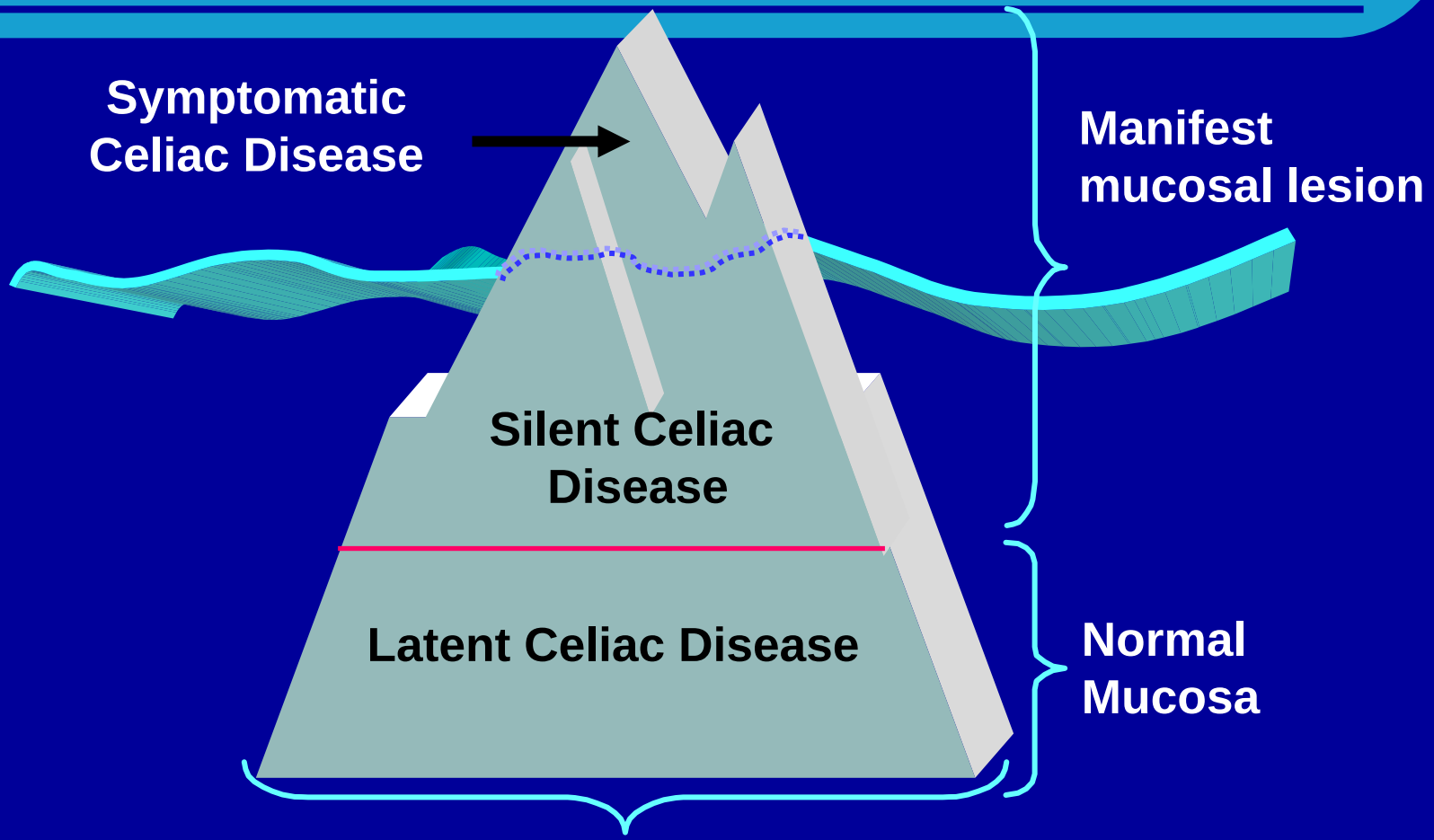
2005
UPDATE

Celiac Disease

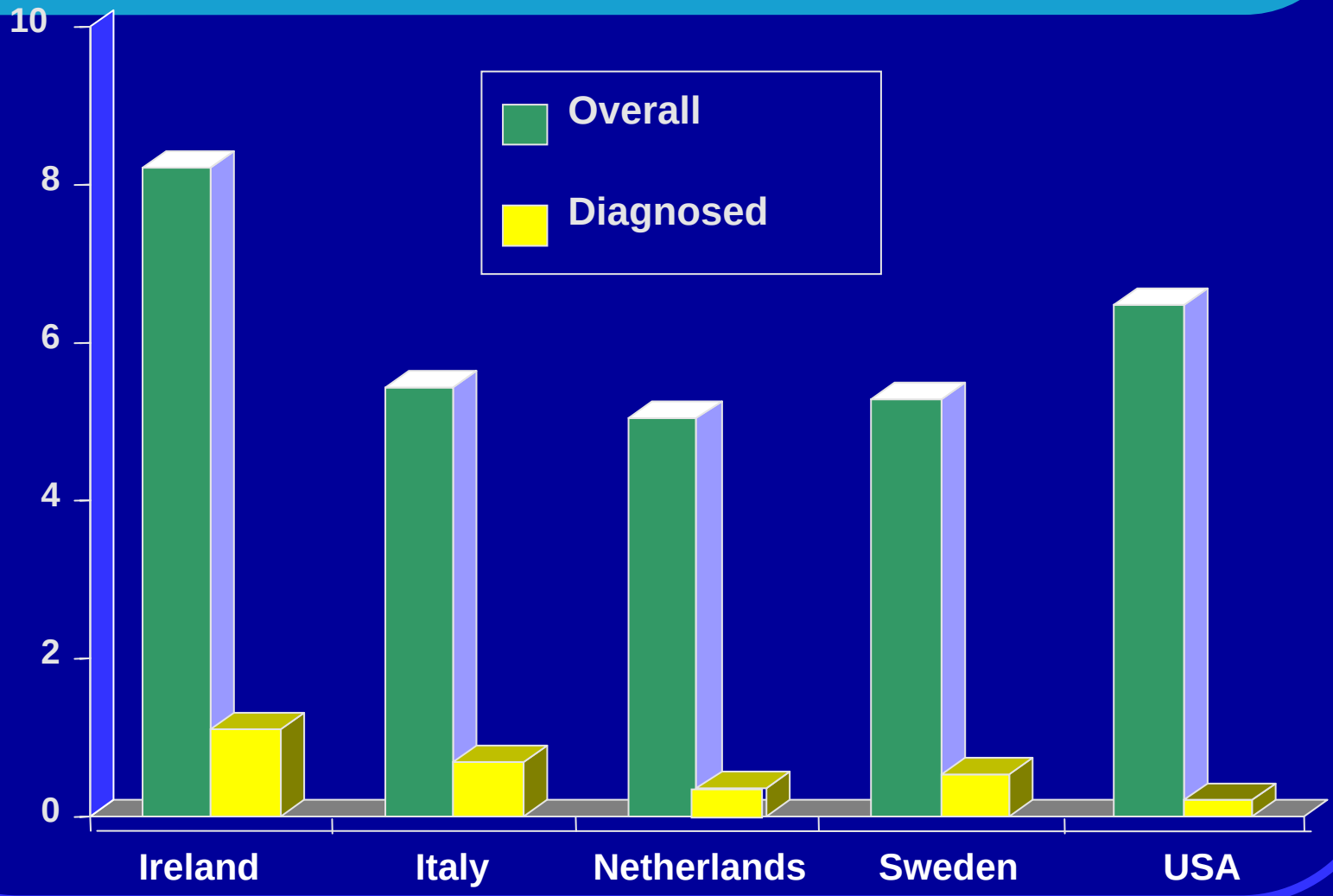
The Problem

- Immune-mediated ENTEROPATHY
  - Chronic inflammation
    - Villous atrophy, Malabsorption
- Permanent sensitivity to GLUTEN
  - Wheat, barley, rye
- Variable clinical manifestations
  - GI and extra-intestinal morbidity
- Treatable
  - Lifelong gluten-free diet
- UNDERDIAGNOSED

The Celiac Iceberg



Celiac Disease Icebergs



Prevalence

- 0.5-1% of general population
  - US and European data
- In children age 2.5-15 y
  - 1:80-1:300
  - Increased 2-10 times in children with GI sx
- In first degree relatives
  - 5-10%
  - Sibling concordance: 7-20%
    - Up to 40% if share high risk HLA haplotype (DQ2 or DQ8)

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%

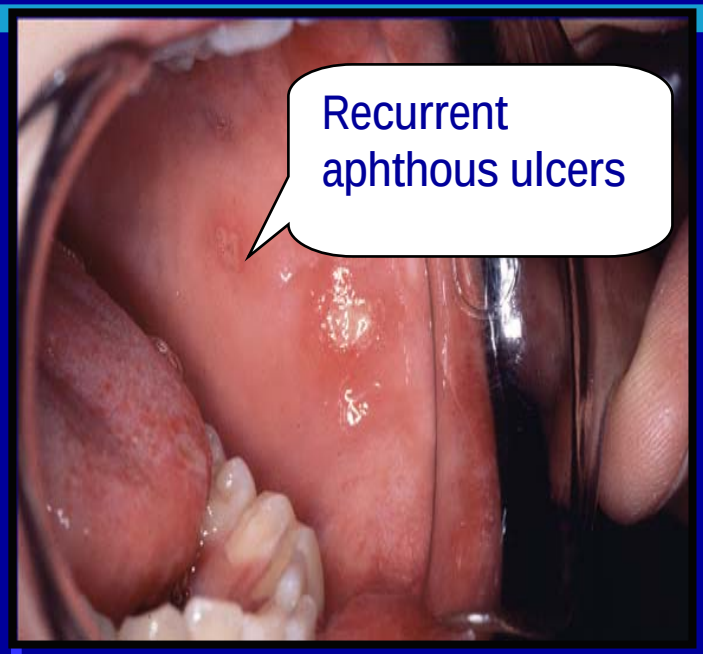
CD Associated Genetic Disorders

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

-- Check TTG IgG
- TTG IgA will be negative
- IgA with celiac serology in all symptomatic children

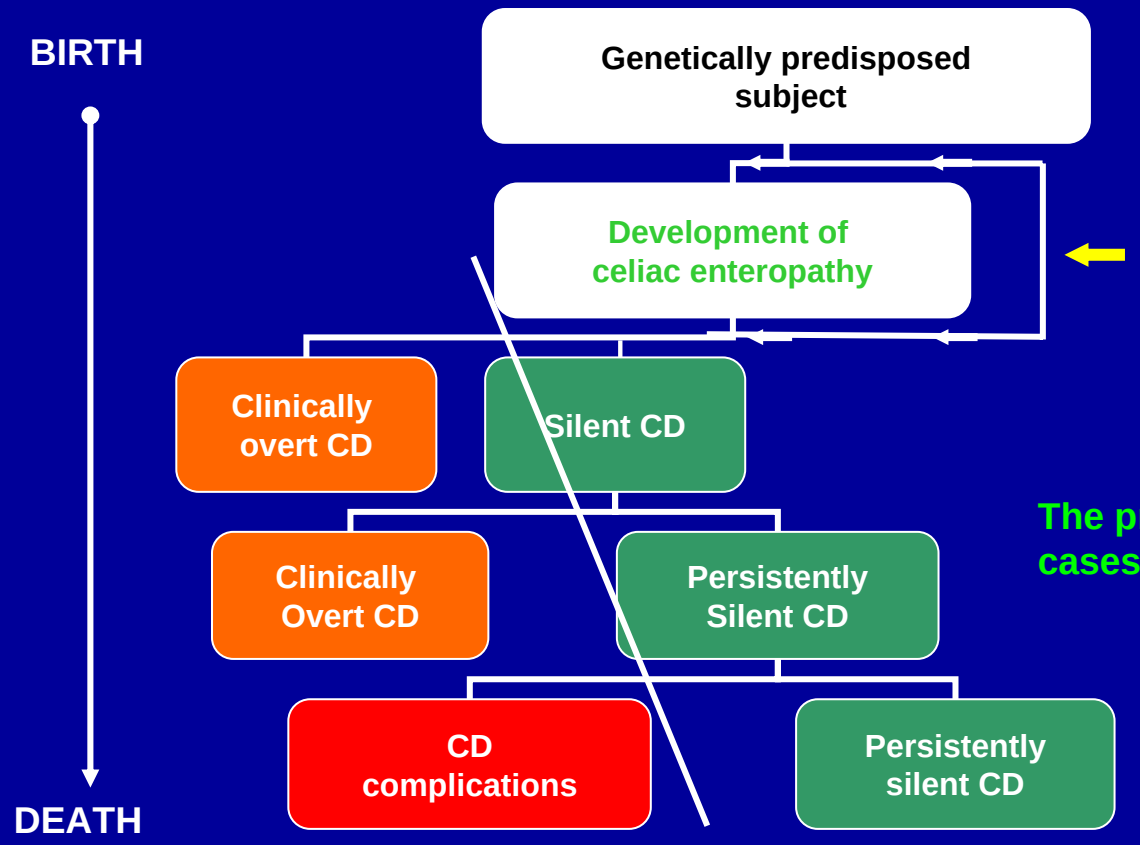
Classical celiac disease

Clinical Manifestations



Dermatitis herpetiformis

Natural history



ENVIRONMENTAL TRIGGERS

Gluten "load"
Intestinal infections
Pregnancy
Cancer

The proportion of symptomatic cases increases with age

Major Complications

- Short stature
- Osteoporosis
- Fertility problems
  - Pubertal delay/amenorrhea
  - LBW/preterm delivery
- Neuropathy
  - Ataxia, seizures, peripheral
- Nutritional deficiencies
  - ADEK, B12, folate, Ca, Zn, EFA
- Chronic Fe-def. anemia
- Increased autoimmunity
- Arthropathy
- Ulcerative jejunitis
- Cancer
  - EAT lymphoma (NHL)
  - Adenocarcinoma
  - Papillary thyroid
  - Melanoma

Testing Recommendations

- Symptomatic children
  - Persistent diarrhea
    - AP, N/V, constipation, anorexia, bloating
  - Undernutrition
    - FTT, poor wt gain
  - EXTRAINTESTINAL

A) Manifestations for which there is strong to moderate evidence
Dermatitis herpetiformis
Dental enamel hypoplasia of permanent teeth
Osteopenia/Osteoporosis
Short stature
Delayed puberty
Iron-deficient anemia unresponsive to treatment with oral iron (*well documented in adults only*)
B) Manifestations for which the evidence is less strong
Hepatitis (elevated liver enzymes)
Arthritis
Epilepsy with occipital calcifications

- Asymptomatic, at-risk
  - 1st degree relative
  - T1D
  - Autoimmune thyroiditis
  - Down
  - Turner
  - Williams
  - Selective IgA deficiency

Serological Test Comparison

Inferior accuracy

	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

PPV near 100% in symptomatic pts

Observer dependent

Recommended

Farrell RJ, Kelly CP. *Am J Gastroenterol* 2001;96:3237-46.

Tissue Transglutaminase (TTG)

- Normal gut enzyme released during injury and
  - stabilizes the cross-linking of proteins in granulation tissue
- Role in Celiac Disease
  - Modification of gliadin epitopes
  - Autoantibodies against TTG correlate with active Celiac Disease

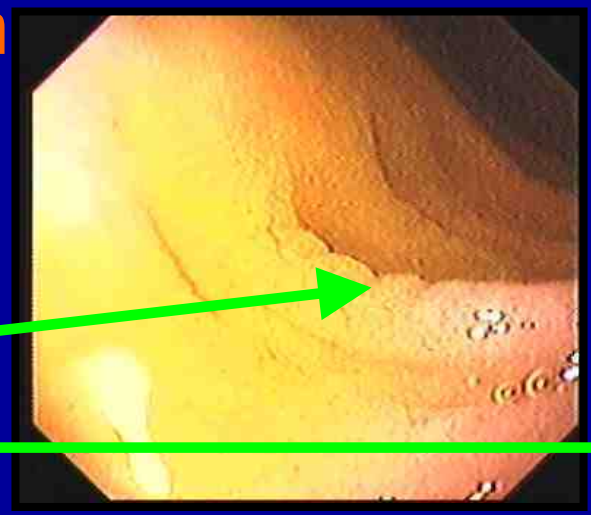
    ? involved in pathogenesis

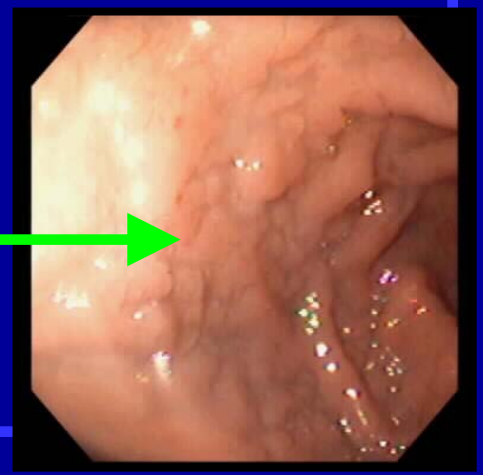
Endoscopy

- Indications
  - Seropositive
  - Seroneg.,symptomatic
- Bx distal duodenum
- Multiple sites
  - Absence of folds
  - Scalloped folds
  - Nodularity
  - Mucosal “mosaic”

Normal

SB Biopsy is still Gold Std for Dx of CD

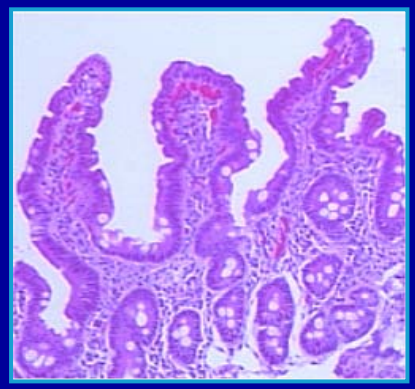




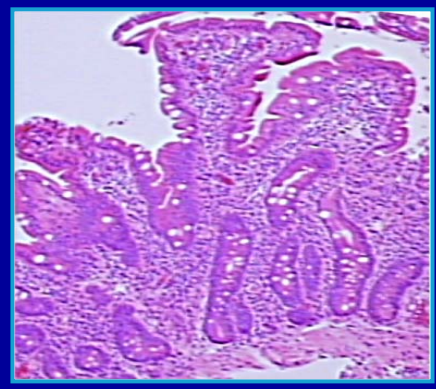
Histopathology

Marsh Classification

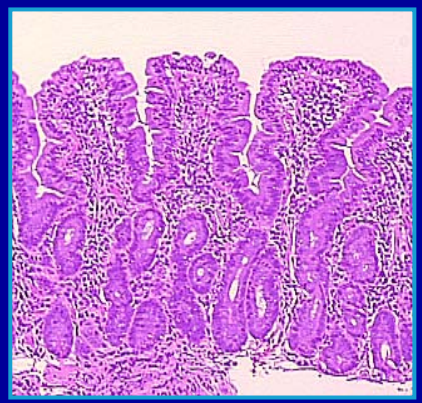
Normal 0



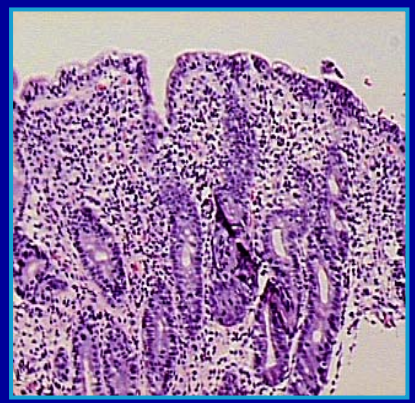
Infiltrative 1



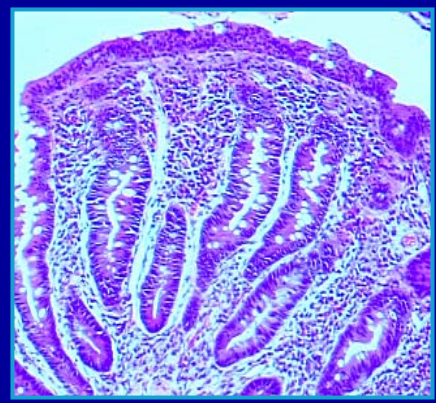
Hyperplastic 2



Partial atrophy 3a



Subtotal atrophy 3b

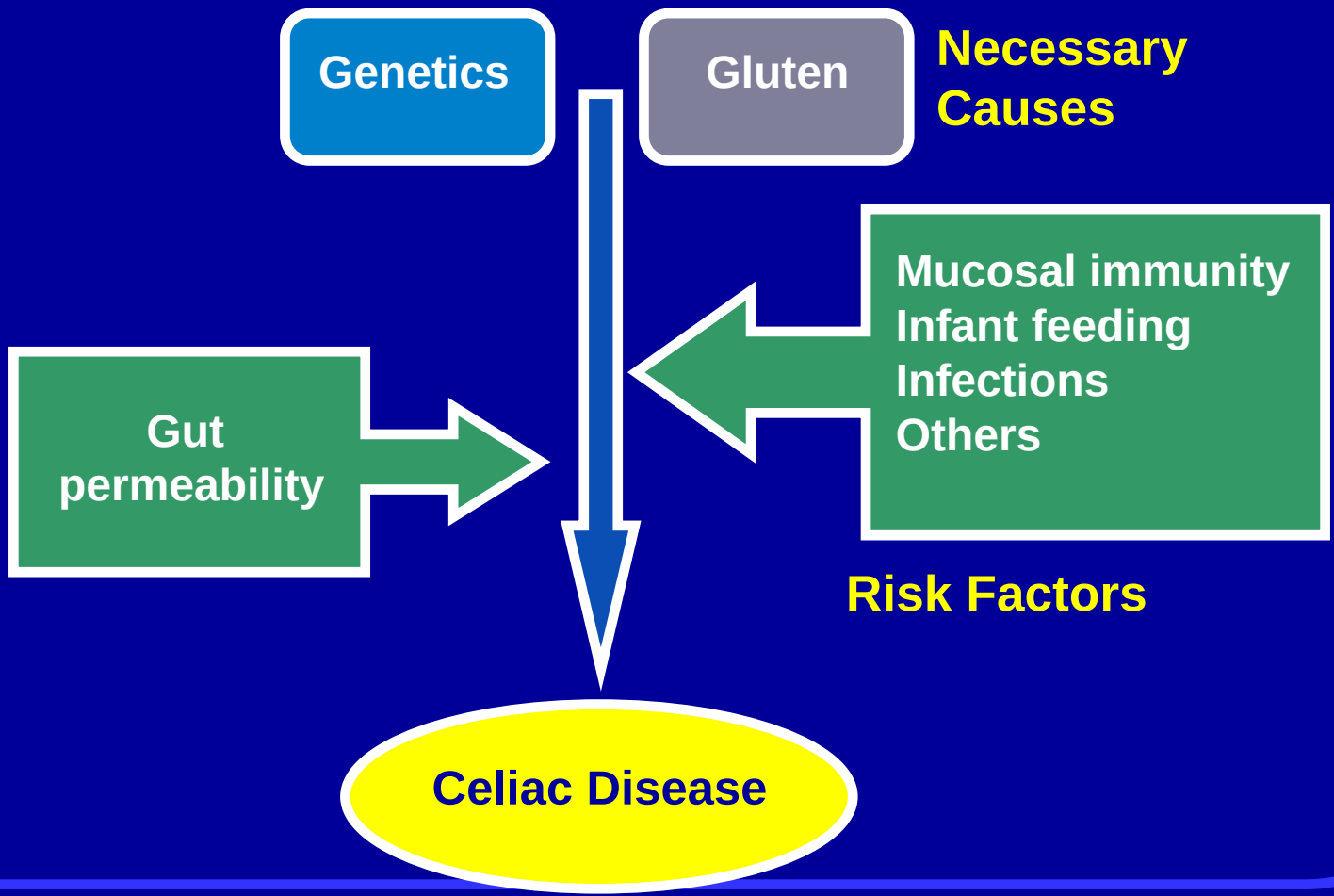


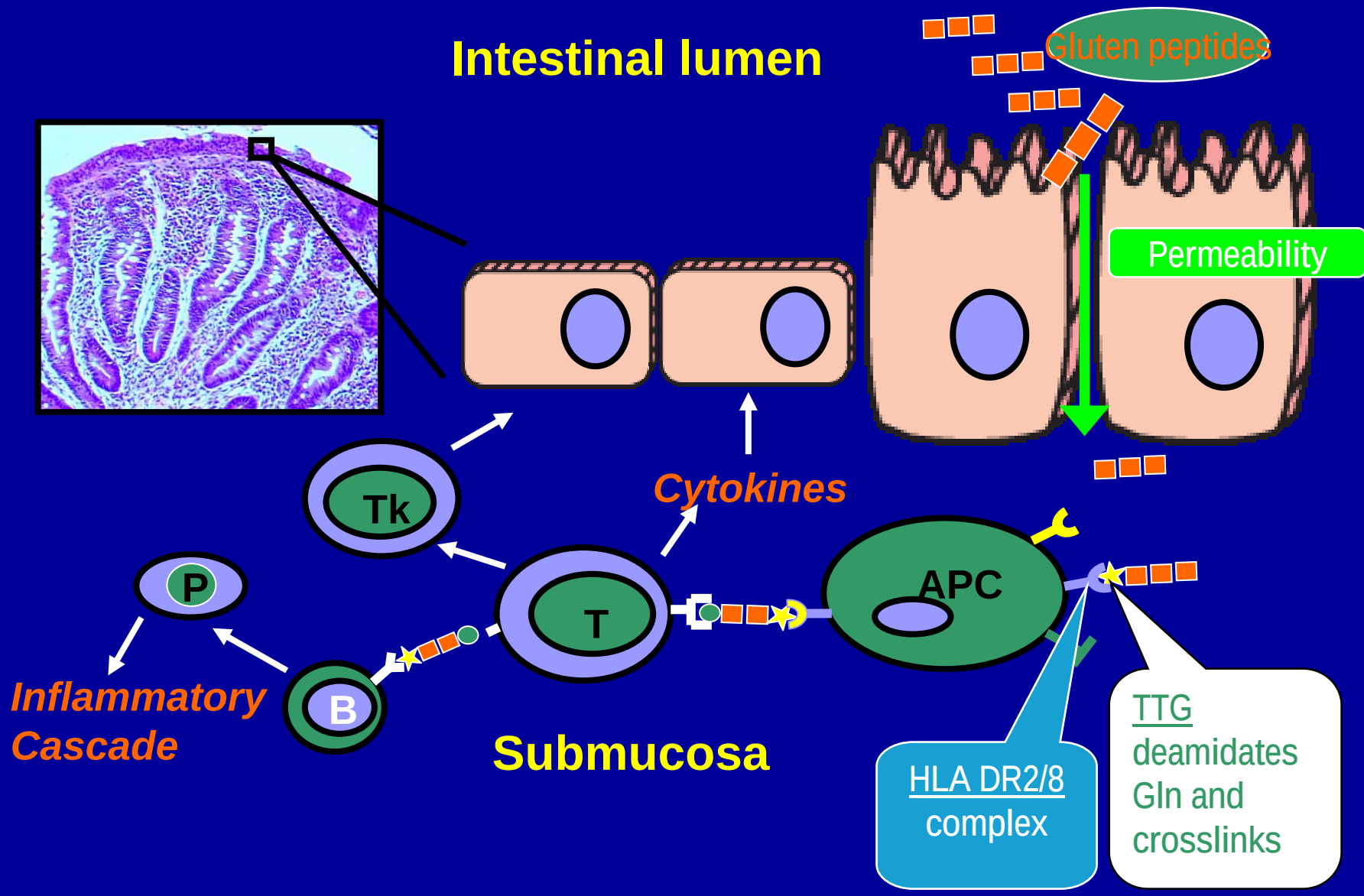
Total atrophy 3c

HLA typing

- HLA DQ2 or DQ8
  - MHC II region on chromosome 6
    - HLA-peptide complex recognized by CD4+ T cell receptors
  - Necessary but not sufficient to develop CD
- High sensitivity, low specificity
  - Negative result virtually excludes CD
    - Screening asymptomatic pts in at-risk groups
    - Equivocal histology

Pathogenesis

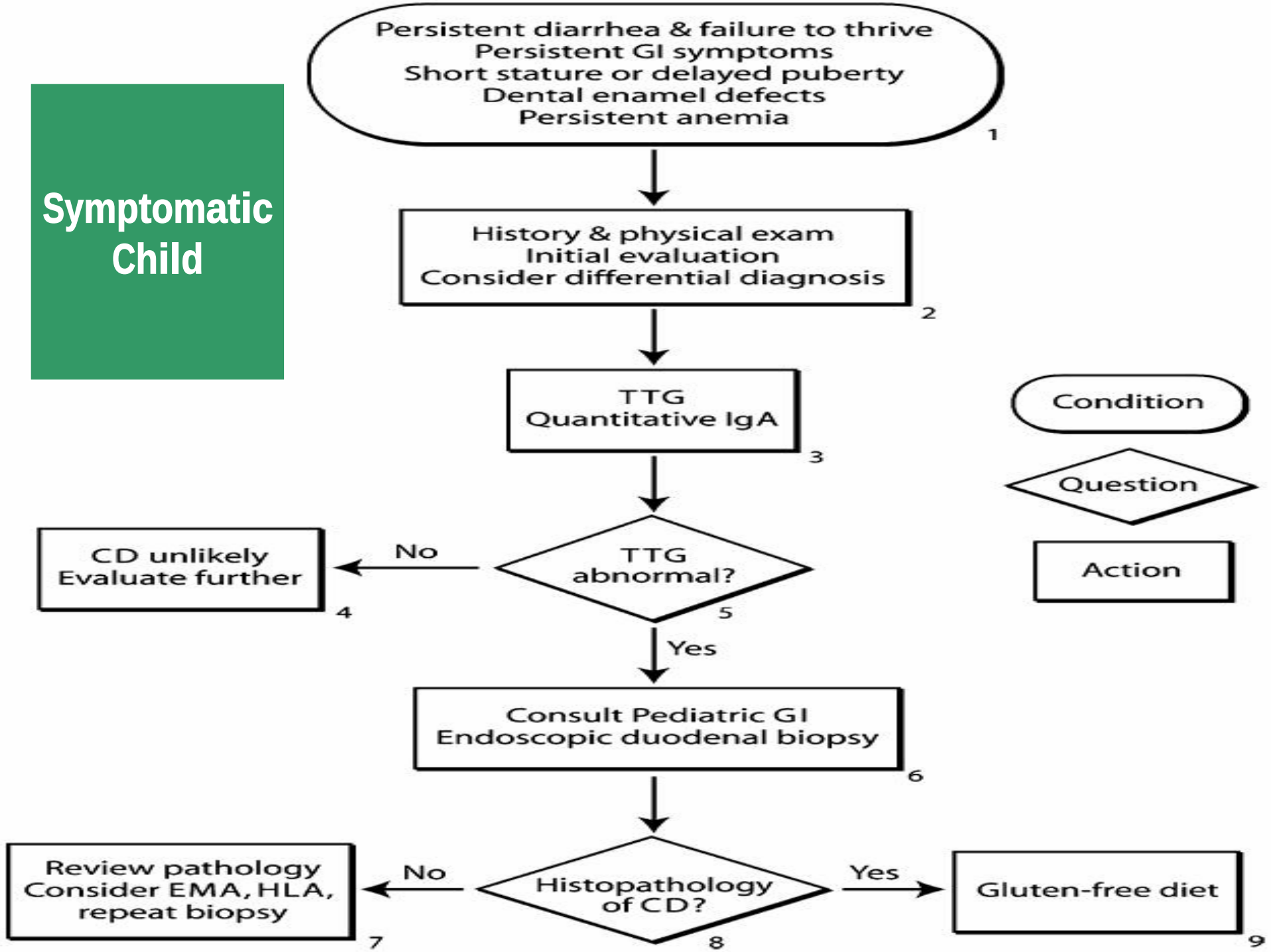


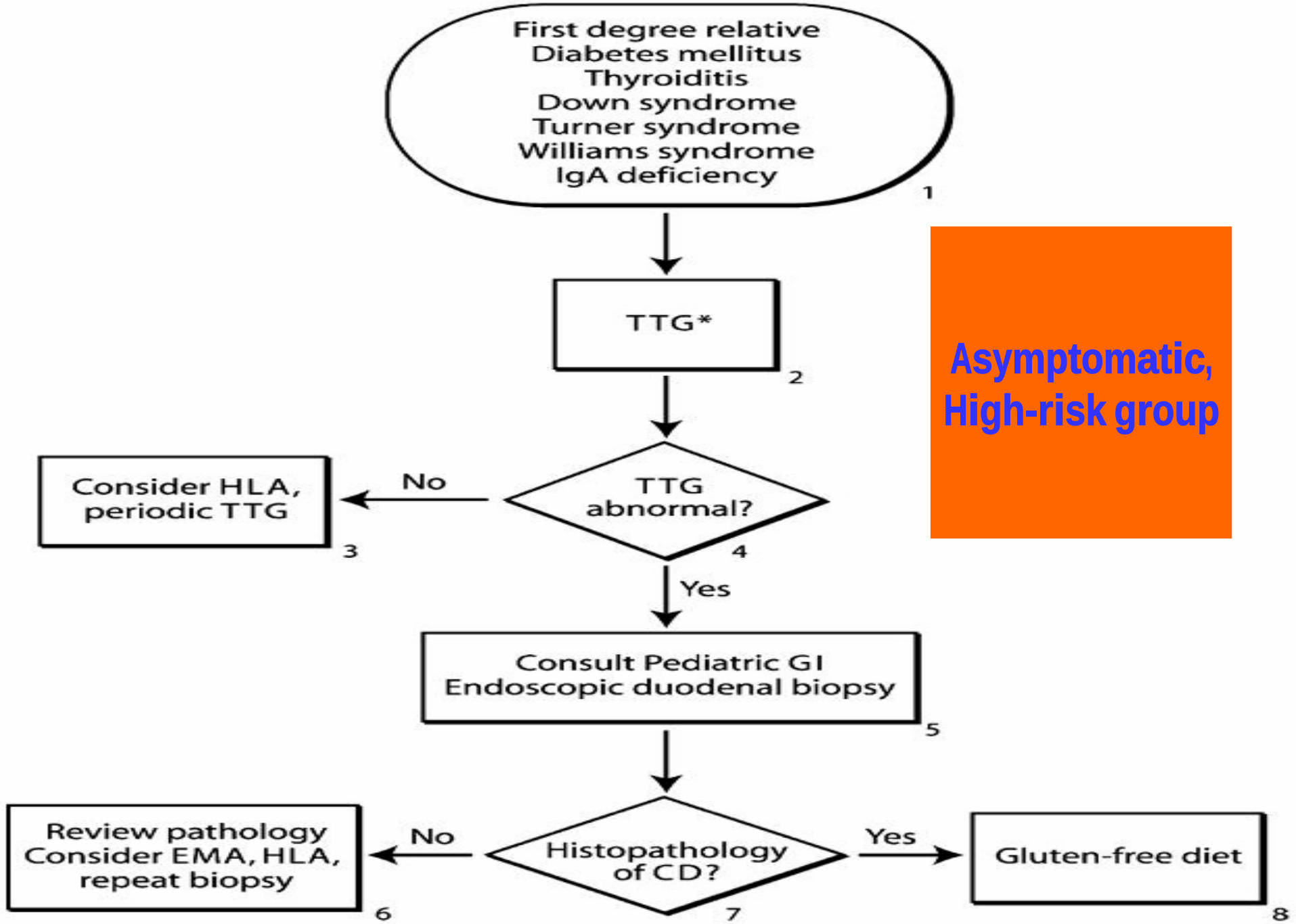

Intestinal lumen
Gluten peptides
Permeability
Tk
Cytokines
P
T
APC
Inflammatory
Cascade
B
Submucosa
HLA DR2/8
complex
TTG
deamidates
Gln and
crosslinks

Treatment

- Lifelong gluten-free diet
- Establish dx first
  - Symptomatic, bx-proven
  - Asx, high-risk, bx-proven
- Early tx benefits
  - Resolution of GI sx
  - Improved growth
  - Reduced cancer risk
- ADA recommendations
  - <200 mg/kg gluten = GFD
  - Malt harmful, oats safe
  - Lactose usually tolerated in early CD
  - Supplement folate, Ca/vitamin D

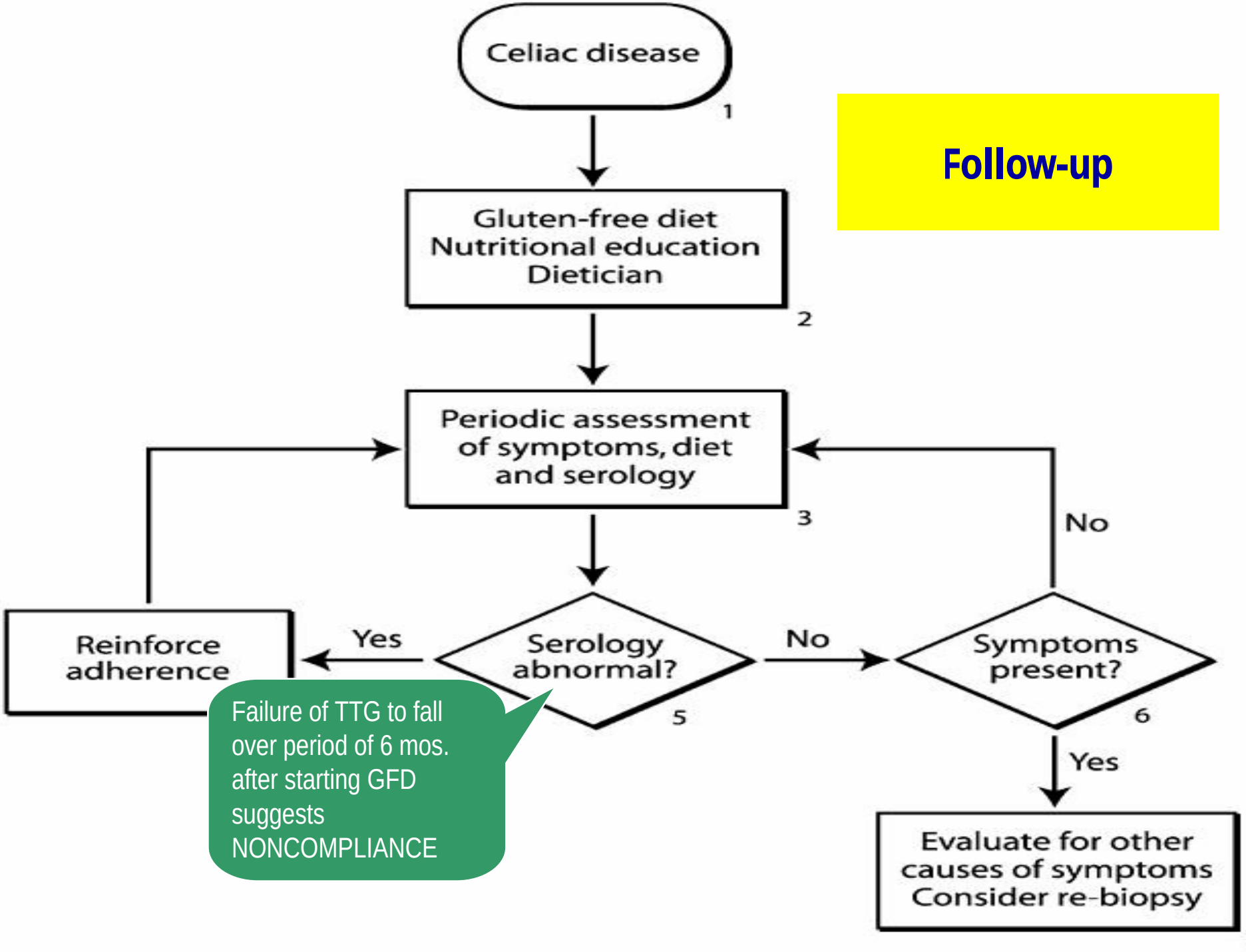
Symptomatic Child



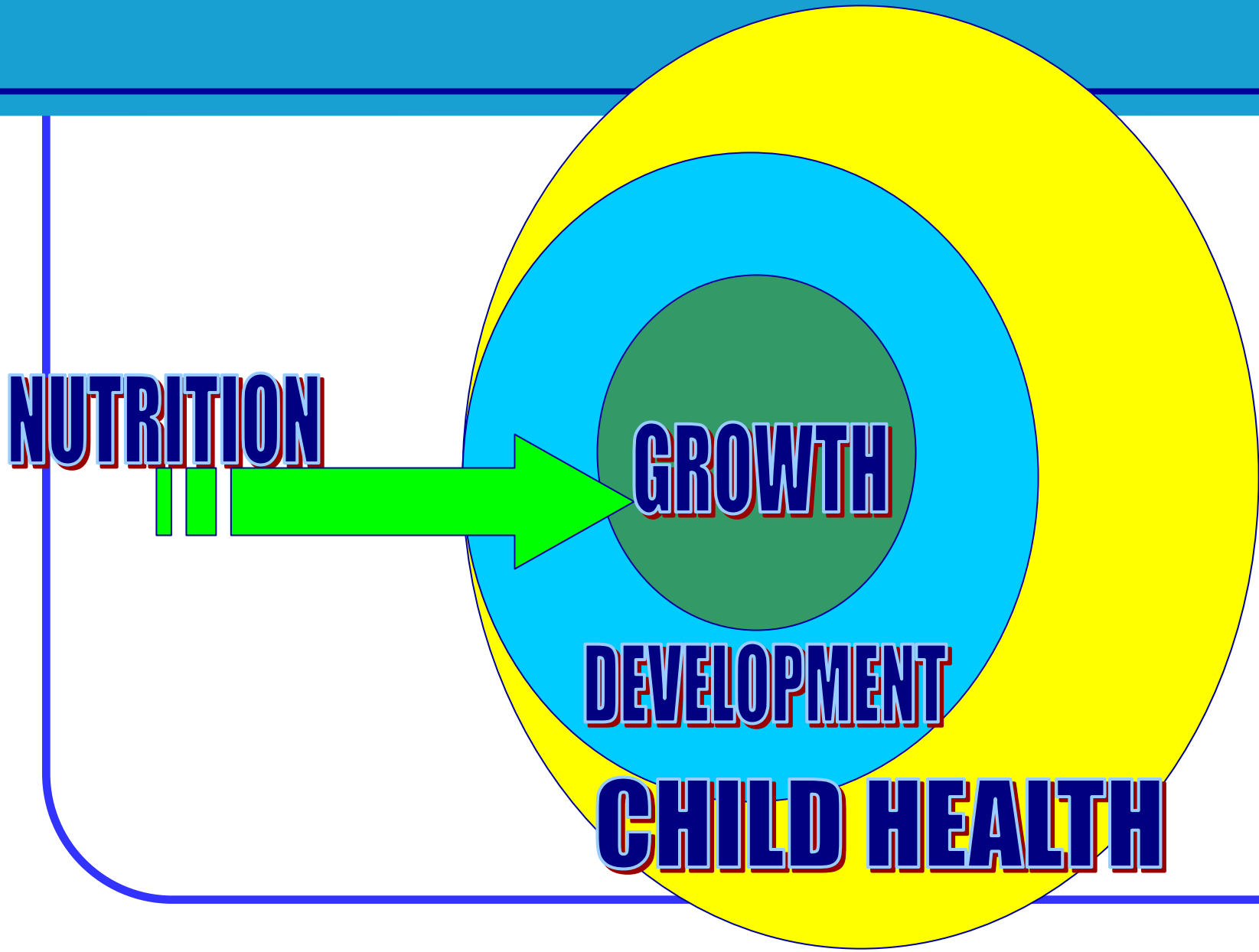


*TTG IgG is recommended for individuals with known IgA deficiency.

Follow-up


Celiac disease
1
Gluten-free diet
Nutritional education
Dietician
2
Periodic assessment of symptoms, diet and serology
3
No
Reinforce adherence
Yes
Serology abnormal?
5
No
Symptoms present?
6
Yes
Failure of TTG to fall over period of 6 mos. after starting GFD suggests NONCOMPLIANCE
Evaluate for other causes of symptoms
Consider re-biopsy

Dr. W.K. Dicke, Dutch pediatrician who discovered the link between gluten grains and celiac disease in the 1950s


NUTRITION
GROWTH
DEVELOPMENT
CHILD HEALTH