The Changing Face of Celiac Disease

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OVERVIEW

Brief Background on the Basics

Changing Face

1. **Autoimmune Nature and Impact**
2. **Diagnosis**

   Does everyone need a biopsy?

   Should genetic testing be done routinely?
3. **Management**

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CELIAC DISEASE: the Basics

Permanent intolerance to gliadin

a protein in wheat, barley and rye

Genetic predisposition

Injury is imunologically mediated

Affects about 1% of the world population

Only about 15-20% of cases are diagnosed

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Autoimmune Pathogenesis

Inappropriate T Cell Response

Requires a trigger

α-gliadin protein from gluten

Requires a genetic predisposition

Strongly associated with an HLA region

characteristic HLA type (HLA-DQ2 & DQ8)

95% of celiac patients

35% of general population

Specific gene(s) for CD has not yet been found

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Current Understanding

Gliadin protein taken up by the intestine

HLA-DQ2 binds gliadin – starts the autoimmune process

Facilitates connection of Ag presenting cell to helper T cell - *considered to be the central event*

This connection starts the immune cascade ->

specific autoantibodies + cell signaling proteins (cytokines)

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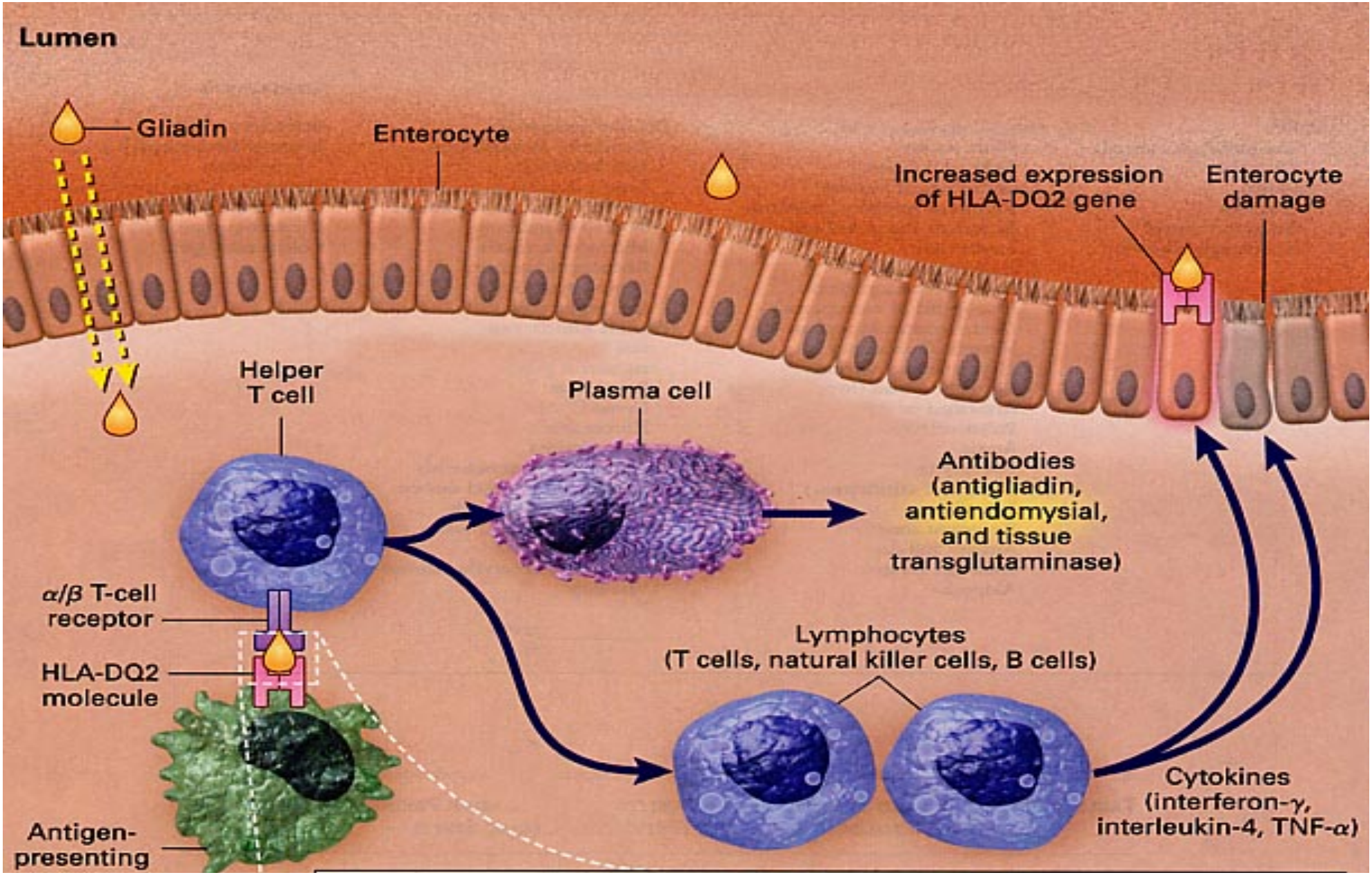

Ferrell NEJM 2002;346:180

Current Understanding

Strong specific HLA association overlaps with other autoimmune diseases

Alteration in immune response can lead to injury to other targets

An altered immune response may be caused by: *differences in the genes*

sequence of events that trigger inflammation

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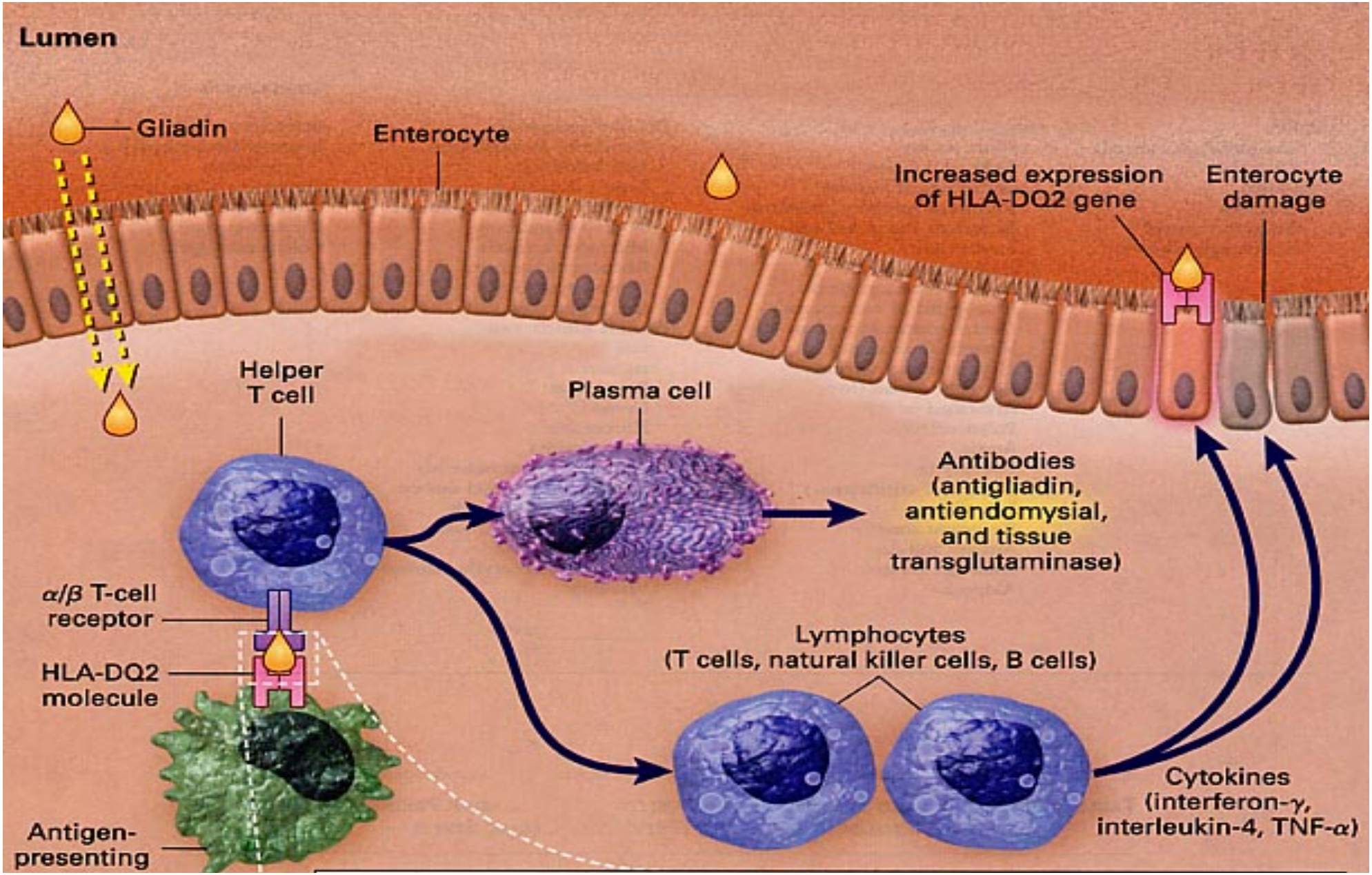

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What is the Impact?

Associated Autoimmune Diseases * Type 1 Diabetes (insulin dependent) * Hypothyroidism * Hyperthyroidism (Grave's Disease) * Secondary Hyperparathyroidism * Sjogren's Syndrome * Addison's Disease * Dilated (congestive) cardiomyopathy ?? * Alopecia Areata – patchy hair loss * Rheumatoid Arthritis * Fibromyalgia * Collagen-Vascular Disease * Multiple Sclerosis * Systemic Lupus Erythematosis * Reynaud's Syndrome	**Behavioral/Psychiatric** * Depression * Attention Deficit Disorder (ADD)/AD Hyperactivity Disorder (ADHD)/Autism * Hypochondria * Inability to concentrate, "brain fog" * Anxiety * Neurosis * Moodiness * Obsessive-Compulsive Disorder **Cancers** * Intestinal lymphoma, non-Hodgkin's lymphoma * Small intestinal adenocarcinoma * Melanoma * Endocrine, thyroid, esophageal malignancies
Dermatologic and Mucous Membranes * Dermatitis Herpetiformis * Eczema * Psoriasis * Vitiligo * Acne * Rosacea * Urticaria – hives * Vasculitis **Hematologic** * Anemia * Leukopenia (low white blood count) * Thrombocytopenia (low platelet count) * Thrombocytosis (increased platelet count) * Bruising * Vitamin K deficiency * Bleeding	**Gastrointestinal** * Diarrhea * Lactose intolerance * Abdominal distention * Wasting * Change in appetite * Constipation * Dyspepsia – "stomach aches" * Bacterial overgrowth * Malabsorption * Flatulence * Reflux/heartburn * Hepatitis – elevated liver function tests * Bloating * Ulcers * Vomiting * Aphthous stomatitis – canker sores
Neurological * Peripheral Neuropathies * Paraplegia * Ataxia – balance disturbance * Seizures * Migraines/headaches * Brain Atrophy and Dementia	**Nutritional** * Weight loss * Stunted growth * Poor weight gain ("failure to thrive") * Low blood sugar **Renal** * IgA Nephropathy
Reproductive * Premature menopause * Infertility * Abnormal menstrual cycles * Spontaneous miscarriage * Delayed puberty **Respiratory** * Respiratory problems * Asthma	**Skeletal** * Osteoporosis/Osteopenia * Joint, bone, muscle pain * Dental enamel defects * Clubbing **Other Symptoms** * Edema * Tetany – spasms of hands * Fatigue, Chronic Fatigue Syndrome * Swelling and inflammation, chronic infections * Night blindness

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Changing Face of Diagnosis

Initial Serology

Quantitative IgA

IgA antibodies:

anti-tissue transglutaminase (tTG)

(anti-endomysial)

Highest positive predictive value >90%

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New ESPGHAN Proposal for Dx

Initial cut-off:

10x or greater increase in IgA anti-tTG

symptomatic (listed 16 possibilities)

Their protocol calls for additional testing:

IgA anti-endomysial Ab

HLA DQ2 and DQ8 testing

If all tests are positive -> diagnosis 'confirmed'

No EGD and biopsy would be done

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2 Important Questions Arise

Will some children have incorrect diagnosis?

Does endoscopy provide other important information?

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Will Incorrect Diagnoses Occur?

Canadian registry: 17,505 children screened

IgA anti tTG Ab -> 775 were pos

Endomysial Ab routinely done in Canada for + tTG

223 patients fit ESPGHAN criteria

4 of these pts had negative biopsies

2% false positive rate

Butzner et al Am J Gastroenterol. 2015;110:760

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Will Biopsies Show Other Diagnoses?

Dr. Stefano Guandalini, U Chicago – DDW 2014

10% of duodenal, gastric or esophageal biopsies obtained from children with ‘non-bx’ criteria showed other diseases

Dr. Peter Green, Columbia – DDW 2014

12% of duodenal, gastric or esophageal biopsies obtained from adults with ‘non-bx’ criteria showed other diseases

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HLA Typing

HLA testing

- ~35% of population has DQ2 or DQ8
- 'Positive' test has little meaning
- Expensive
- Insurance does not always cover the test

Value of negative HLA testing

- High negative predictive value
- If DQ2/DQ8 negative, only ~ 2 % chance of CD

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Changing Face of Management

Management

Many sets of guidelines for CD exist but effective long-term management programs are lacking

Little consensus on how best to follow patients

We hosted a group of 6 experts in pediatric CD:

to review the published studies

develop evidenced-based Best Practices

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Experts

Decker Butzner, U. of Calgary	*Bone disease*
Amy DeFelice, Columbia	*Liver issues*
Alessio Fasano, Harvard U	*Testing*
Stefano Guandalini, U Chicago	*Hematology*
Edwin Liu, U. of Colorado	*Endocrine problems*
Kim Newton, UC San Diego	*Nutritional issues*
John Snyder, CNHS	*Organizer*

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Methods

Over 600 papers reviewed

Each expert chosen to summarize 1 area

33 best practice issues chosen for evaluation

Anonymous voting on questions for each issue

Consensus defined as > 70% agreement

consensus reached for 32 of 33 questions

unanimous agreement for 20 of 33

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Consensus Best Practices

BONE	**Initial**	**F/U**
Routine screening for bone health (labs, imaging)	**No**	**No**
Routine screening for vitamin D status	**Yes**	**-**
Screening selected pts with risk factors of bone dis	**Yes**	**Yes**
HEMATOLOGY		
Routine screening for anemia	**Yes**	**Yes**
Routine screening for folate deficiency	**No**	**No**
ENDOCRINE		
Routine screening for type 1 diabetes	**No**	**No**
Routine screening for thyroid disease	**Yes**	**Yes**

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Consensus Best Practices

	Initial	F/U
LIVER		
Routine screening for ALT and AST	**Yes**	-
NUTRITION		
Routine assessment of WT, HT, BMI	**Yes**	**Yes**
Access to an experienced dietitian	**Yes**	**Yes**
Routine vitamin supplementation	**Yes**	**Yes**
TESTING		
Routine IgA anti-tTG Ab test at 3-6 mo post dx	-	**Yes**
Routine tTG Ab to monitor compliance with GFD	**Yes**	-
Use of endomysial Ab limited to pts with AI disease	**Yes**	**Yes**

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Conclusions

Changes related to autoimmune nature

- better understanding of the genes and genetic factors
- better understanding of the sequence of events required

Changes related to diagnosis

- serology holds promise but requires further fine-tuning
- endoscopy still considered the 'gold standard'
- HLA testing is more helpful if it is negative

Changes related to follow-up

- Best Practices will hopefully provide a more thoughtful framework for management

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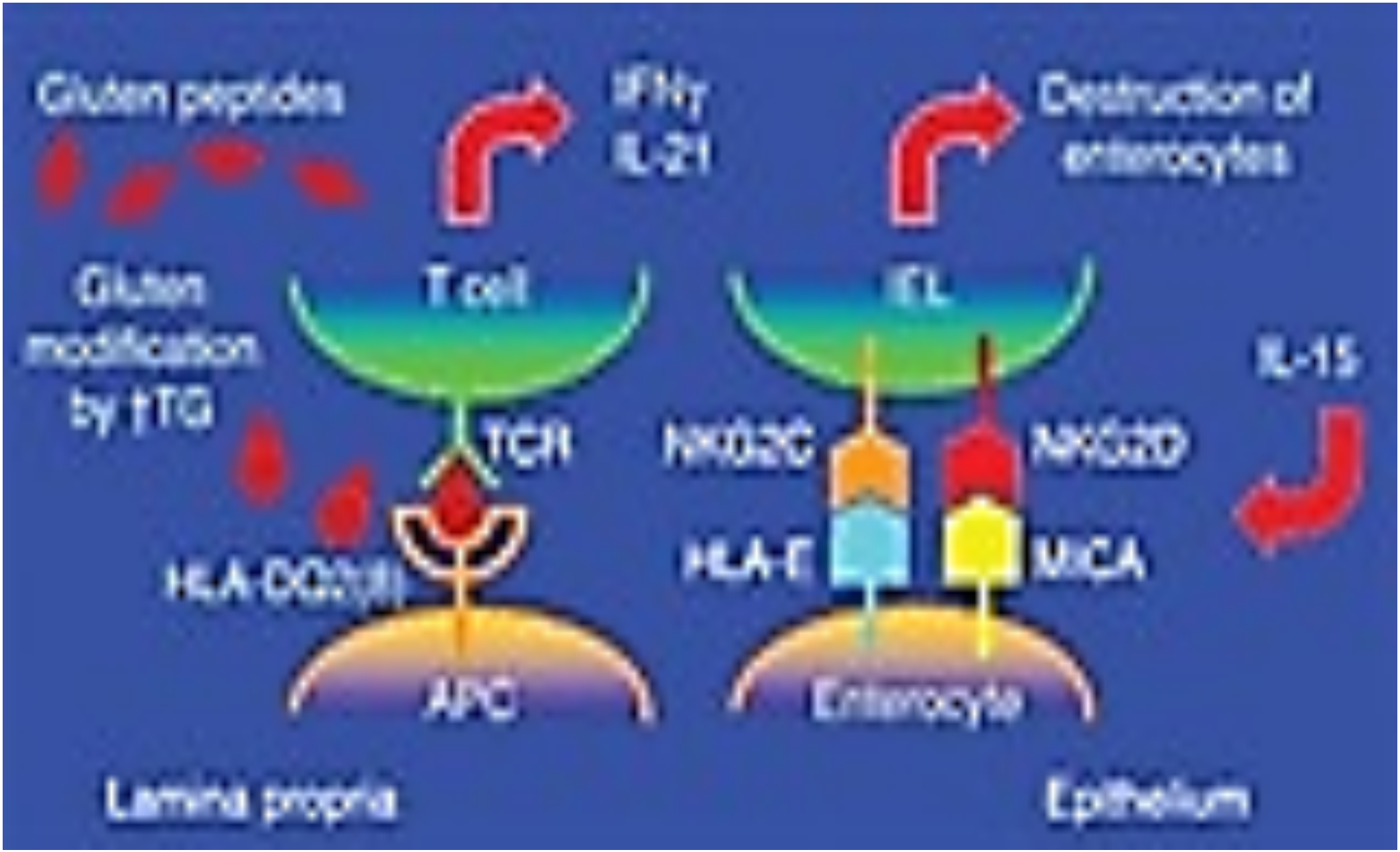
CD, Gluten Sensitivity, Wheat Allergy

Variable	Celiac Dis	Glut Sens	Wheat Aller
Time: expos to symptoms	wks to yrs	hrs to days	min to hr
Pathogenesis	Autoimmune innate + adapt	Possible innate	Allergic immune resp
HLA antigen	Most are DQ2 or DQ8 pos	No role	No role
Enteropathy	Almost always	Never	Never (eos)



Koning JPGN 2014;59:S1