

# Review of Recent Studies



**Children's National**™

***John Snyder, MD***

# 3 Categories

**Feeding Practices**

**Policy: new government reports**

**New Treatments**

# Feeding Practices

# Impact of Infant Feeding Practices on Development of CD

Celiac disease has  markedly in recent decades

Seroprevalence studies indicate that this is a true rise  
- not caused by increased awareness and testing

Prior studies have suggested that infant feeding practices and timing of initial gluten exposure play central roles in the development of CD

*Am J Gastroenterol. 2016;111:12-4.*

# Impact of Infant Feeding Practices

## 2 Studies Reviewed

**Lionetti E et al. NEJM 2014;371:1295**

20 centers throughout Italy

compared introduction of gluten at 12 mo vs 6 mo

553 children with HLA DQ2 or DQ8h and 1<sup>st</sup>

degree relative with celiac disease.



# Impact of Infant Feeding Practices

## 2 Studies Reviewed

**Vriezinga SL. NEJM 2014;371:1304**

Hypothesis: early gluten exposure creates tolerance

Double-blind placebo-controlled trial

Conducted in 8 countries

Introduced small amounts of gluten at 4 mo

944 infants

at-risk HLA DQ2/DQ8 + 1<sup>st</sup> degree relative with CD

Received either 200 mg of gluten or placebo

Dietary gluten introduced at 6 mo



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# Impact of Infant Feeding Practices Findings

**2 multicenter randomized trials tested strategies  
on early or delayed gluten introduction in infants**

**Neither strategy appeared to influence CD risk**

**Breastfeeding did not protect against  
development of CD**

***Am J Gastroenterol. 2016;111:12-4***  
***Commentary by leaders of NASSCD***

# Is G-F Diet Healthy for non-CD?

**Commentary by Norelle Reilly, Columbia**

**Reviewed:**

rapid rise of use of gluten-free diet

lack of inherent toxicity of gluten for non-CD

potential for nutrient deficiencies due to fewer  
enriched foods

**Emphasizes importance of utilizing a dietitian**

***J Pediatr. 2016.04.014***



**Policy**

# Policy - New Review of CD

Agency for Healthcare Research and Quality - DHHS

Mandate: provide systematic science-based reviews to improve quality of health care in US

2/1/2016 first-ever evidence review on diagnosis of celiac disease

Provides a thorough assessment and rating of diagnostic tests

[www.ahrq.gov](http://www.ahrq.gov)

# Impact of Review - CDF

1. Provides focus on low diagnosis rate for CD (~20%)
2. Represents Federal Government recognition that the low diagnosis rate is adversely impacting public health
3. Increased awareness of CD

AHRQ will release a Clinician Summary

will provide a federally sanctioned working document that explains celiac disease, presenting symptoms, and suggested tests to confirm diagnosis

[www.celiac.org](http://www.celiac.org)

# FDA: Arsenic in Rice

**Arsenic (As)** is an element in the Earth's crust

*Present in water, air and soil*

*Fertilizers and pesticides also contribute to levels*

**Exists in 2 forms, organic and inorganic**

*Inorganic arsenic is more toxic in the diet*

**Rice has ↑ inorganic As**

*rice absorbs arsenic more than other crops*

**As is not intentionally added to rice**

*Cannot be completely removed*

# FDA: *As* in Rice

**New data from FDA [www.fda.gov](http://www.fda.gov); April 2016:  
20-170 ppb arsenic in infant rice cereal  
more 2x that in other infant foods**

**Parents advised to vary the types of cereal  
grains fed to young children**

**FDA–AAP: limit/"action level" of 100 ppb  
for infant rice cereal**



# Take Home

**Arsenic is found 'naturally' in many foods**

**No data provided for consumption of rice products - consumption not considered a health problem**

**Realize that the arsenic content of rice varies**

**Look for rice with As levels  $< 100$  ppb**

# New Therapies

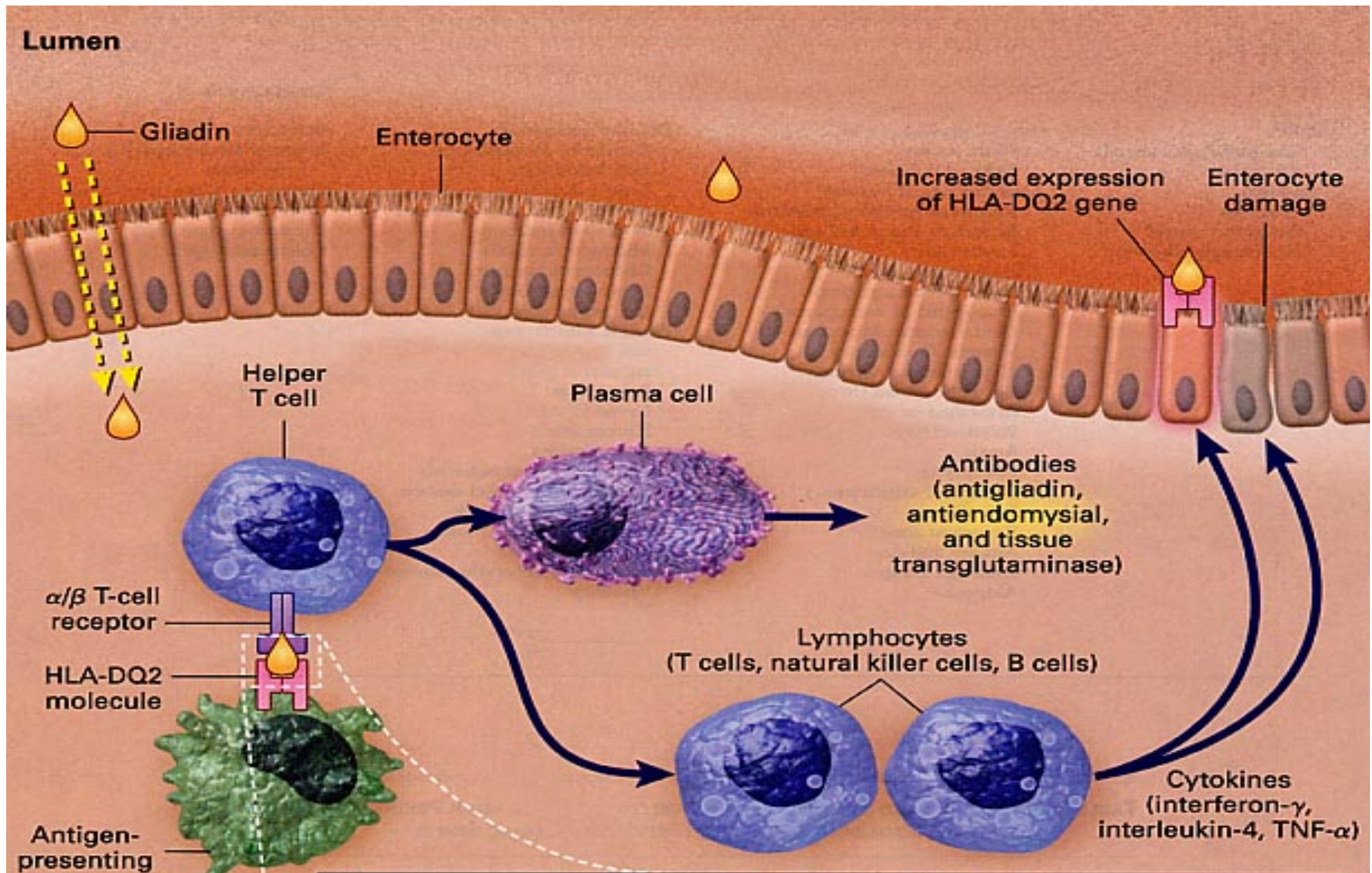
# Background

## **3 major targets for therapies**

- 1. Bind or digest gliadin peptides (part of gluten)**
- 2. Block uptake of gliadin**
- 3. Alter immune response**

***Updates from DDW, May, 2016***





# Binding/Digestion of Gliadin

## **Binding - polymeric resins**

bind to gliadin – prevent release of toxic forms  
clinical trials just beginning

## **Digestion**

**oral enzyme preparations** – problems with  
delivery and stability

**intestinal flora** - that degrades gliadin



# Binding Resin

## **BL-7010 BionlineRx**

polymer with high affinity to gliadins

initial studies in humans and mice have shown  
protection to intestinal mucosa

Now in Phase 1 safety study



# Digestion - Enzymes

## **Alvine Pharmaceuticals - ALV003**

Oral preparation of 2 enzymes

Aimed at patients with symptoms despite GF diet

**Now in Phase 2b trials**



# Digestion - Probiotic

**Theory:** Why do only 3% of DQ2/8 people develop CD?  
Gut flora may modulate gluten-induced injury

## **Mouse model**

chose several common intestinal bugs

**Findings:** Small intestinal bacteria can metabolize  
gluten peptides and impact gluten immunogenicity

***Flavia Verdu, McMaster Univ***

# Block Uptake of Gliadin

## **Lorazotide - Alba Therapeutics**

### **Zonulin receptor antagonist**

Tight junction regulator

1<sup>st</sup> in class oral peptide that prevents tight junction opening

Aimed at patients with symptoms despite GF diet

Not as big an impact on permeability as hoped

No apparent impact on uptake across the cell

**About to enter phase III trials**



# Alter Immune Response - Vaccine

**Nexvax2®:** consists of 3 peptides recognized by gluten-reactive CD4+ T cells in HLA-DQ2 CD pts

**Attenuates responsiveness to gluten peptides**

**Aims to restore immune tolerance to gluten**

**Intradermal injections each week**

**Robert Anderson, ImmusanT, Inc, Cambridge,  
MA**

# Alter Immune Response - Vaccine

**Preliminary data indicate that weekly vaccinations will be required for many weeks**

**May be analogous to allergy shots**

**Now in phase 1 trials**



# Montelukast (Singulair) Study U Chicago

Trial of Montelukast (Singulair) in celiac disease

Theory: leukotriene receptor antagonist (LTRA)

blocks leukotriene D4 to reduce inflammation

Preliminary research shows that montelukast blocks cytotoxic T cells that stimulate intestinal damage

No data for use in celiac disease

Large body of data on safety

*U Chicago is recruiting adults for the study*





# What is the Impact of CD?

<p><b>Associated Autoimmune Diseases</b></p> <ul style="list-style-type: none"> <li>* Type 1 Diabetes (insulin dependent)</li> <li>* Hypothyroidism</li> <li>* Hyperthyroidism (Grave's Disease)</li> <li>* Secondary Hyperparathyroidism</li> <li>* Sjogren's Syndrome</li> <li>* Addison's Disease</li> <li>* Dilated (congestive) cardiomyopathy ??</li> <li>* Alopecia Areata – patchy hair loss</li> <li>* Rheumatoid Arthritis</li> <li>* Fibromyalgia</li> <li>* Collagen-Vascular Disease</li> <li>* Multiple Sclerosis</li> <li>* Systemic Lupus Erythematosus</li> <li>* Reynaud's Syndrome</li> </ul>	<p><b>Behavioral/Psychiatric</b></p> <ul style="list-style-type: none"> <li>* Depression</li> <li>* Attention Deficit Disorder (ADD)/AD Hyperactivity Disorder (ADHD)/Autism</li> <li>* Hypochondria</li> <li>* Inability to concentrate, "brain fog"</li> <li>* Anxiety</li> <li>* Neurosis</li> <li>* Moodiness</li> <li>* Obsessive-Compulsive Disorder</li> </ul> <p><b>Cancers</b></p> <ul style="list-style-type: none"> <li>* Intestinal lymphoma, non-Hodgkin's lymphoma</li> <li>* Small intestinal adenocarcinoma</li> <li>* Melanoma</li> <li>* Endocrine, thyroid, esophageal malignancies</li> </ul>
<p><b>Dermatologic and Mucous Membranes</b></p> <ul style="list-style-type: none"> <li>* Dermatitis Herpetiformis</li> <li>* Eczema</li> <li>* Psoriasis</li> <li>* Vitiligo</li> <li>* Acne</li> <li>* Rosacea</li> <li>* Urticaria – hives</li> <li>* Vasculitis</li> </ul> <p><b>Hematologic</b></p> <ul style="list-style-type: none"> <li>* Anemia</li> <li>* Leukopenia (low white blood count)</li> <li>* Thrombocytopenia (low platelet count)</li> <li>* Thrombocytosis (increased platelet count)</li> <li>* Bruising</li> <li>* Vitamin K deficiency</li> <li>* Bleeding</li> </ul>	<p><b>Gastrointestinal</b></p> <ul style="list-style-type: none"> <li>* Diarrhea</li> <li>* Lactose intolerance</li> <li>* Abdominal distention</li> <li>* Wasting</li> <li>* Change in appetite</li> <li>* Constipation</li> <li>* Dyspepsia – "stomach aches"</li> <li>* Bacterial overgrowth</li> <li>* Malabsorption</li> <li>* Flatulence</li> <li>* Reflux/heartburn</li> <li>* Hepatitis – elevated liver function tests</li> <li>* Bloating</li> <li>* Ulcers</li> <li>* Vomiting</li> <li>* Aphthous stomatitis – canker sores</li> </ul>
<p><b>Neurological</b></p> <ul style="list-style-type: none"> <li>* Peripheral Neuropathies</li> <li>* Paraplegia</li> <li>* Ataxia – balance disturbance</li> <li>* Seizures</li> <li>* Migraines/headaches</li> <li>* Brain Atrophy and Dementia</li> </ul>	<p><b>Nutritional</b></p> <ul style="list-style-type: none"> <li>* Weight loss</li> <li>* Stunted growth</li> <li>* Poor weight gain ("failure to thrive")</li> <li>* Low blood sugar</li> </ul> <p><b>Renal</b></p> <ul style="list-style-type: none"> <li>* IgA Nephropathy</li> </ul>
<p><b>Reproductive</b></p> <ul style="list-style-type: none"> <li>* Premature menopause</li> <li>* Infertility</li> <li>* Abnormal menstrual cycles</li> <li>* Spontaneous miscarriage</li> <li>* Delayed puberty</li> </ul> <p><b>Respiratory</b></p> <ul style="list-style-type: none"> <li>* Respiratory problems</li> <li>* Asthma</li> </ul>	<p><b>Skeletal</b></p> <ul style="list-style-type: none"> <li>* Osteoporosis/Osteopenia</li> <li>* Joint, bone, muscle pain</li> <li>* Dental enamel defects</li> <li>* Clubbing</li> </ul> <p><b>Other Symptoms</b></p> <ul style="list-style-type: none"> <li>* Edema</li> <li>* Tetany – spasms of hands</li> <li>* Fatigue, Chronic Fatigue Syndrome</li> <li>* Swelling and inflammation, chronic infections</li> <li>* Night blindness</li> </ul>