Autoimmune Enteropathy: My infant patient has intractable diarrhea

Harland Winter MD

Autoimmune Enteropathy: My Infant Patient Has Intractable Diarrhea

NASPGHAN 2010

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Conflicts of Interest

- I have no disclosures relevant to the topic of autoimmune enteropathy. Harland Winter, MD

- Learning Objectives
  - Describe the common clinical presentations and pathologic findings of various autoimmune polyendocrinopathies, including gastrointestinal and non-gastrointestinal presentations
  - Describe the genetic mutations involved in autoimmune enteropathies
  - Describe treatment options in autoimmune enteropathies

Causes of Persistent Diarrhea in Infants

- Misdiagnosis or inadequate treatment of food-sensitive enteropathy
- Immunodeficiency: innate or adaptive
- Anatomic abnormalities
- Dysmotility syndromes
- Inflammatory enteritis or colitis
- Metabolic disorders with enteropathy
- Malabsorption or maldigestion of specific nutrients
- Primary syndrome of intractable diarrhea

Primary Syndromes of Intractable Diarrhea in Infants

- Primary epithelial defects:
  - Microvillus inclusion disease
  - Tufting enteropathy (α6β4 integrin deficiency)
  - Enterocyte heparan sulphate deficiency
  - lack of intestinal enteroendocrine cells caused by loss-of-function by mutations in *NEUROG3*

Primary Syndromes of Intractable Diarrhea in Infants

- Immune-mediated: autoimmune enteropathy
  - Autoantigen is known
    - Autoimmune enteropathy with nephropathy
  - Mutation of immunoregulatory gene
    - Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome
    - Autoimmune-Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APCED) Syndrome
  - T lymphocyte activation deficiencies ($CD3_{\gamma}$ mutation)
  - Unclassified

Key Point

- Infants with epithelial cell defects often present within the first two weeks of life
- Infants with autoimmune enteropathies usually have onset of symptoms after one month of age.

Intractable Diarrhea

- ESPGHAN survey of patients with severe diarrhea:
  - less than two years of age
  - requiring TPN
  - persistent villous atrophy
  - refractory to treatment
- N = 47 and about 50% had anti-enterocyte antibodies, but only 15% had the antibody directed against the brush border.
- Patients with positive AECA tended to have hyperplastic crypts, crypt abscesses, normal or increased intraepithelial lymphocytes.

Goulet OJ et al. JPGN 1998;26:151-161

Autoimmune Enteropathy

- Three different types
  - Type 1: IPEX syndrome: *i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked syndrome
  - Type2: IPEX-like but without mutations in the FOXP3 gene
  - Type 3: Autoimmune manifestations primarily limited to the GI tract

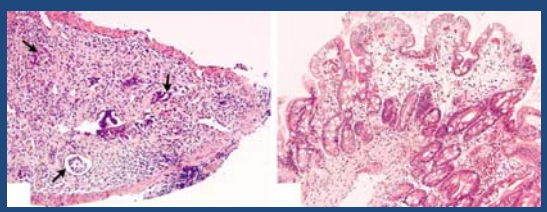
Autoimmune Enteropathy and Nephropathy

- Severe enteropathy
- Relative paucity of intraepithelial lymphocytes
- 75kD autoantigen identified as the intestinal isoform of harmonin, a protein related to zonulin, a molecule that regulates tight junctions and intestinal paracellular permeability
- A mutation in harmonin resulting in loss of function associated with congenital deafness (but without GI symptoms)

IPEX Syndrome

- X-linked
- Intestinal disease is the earliest manifestation
- Gene defect similar to defect in Wiscott-Aldrich syndrome, but platelets are normal
- Mutations found in FOXP3, a control gene of regulatory T cells (Tregs), that lead to absent of dysfunctional Tregs.
- Infiltration of the skin, GI tract with T cells
- Increased levels of autoantibodies against blood, thyroid and pancreatic cells; one report of antibody against 75-kd antigen in intestine and kidney

IPEX Syndrome Small Intestine

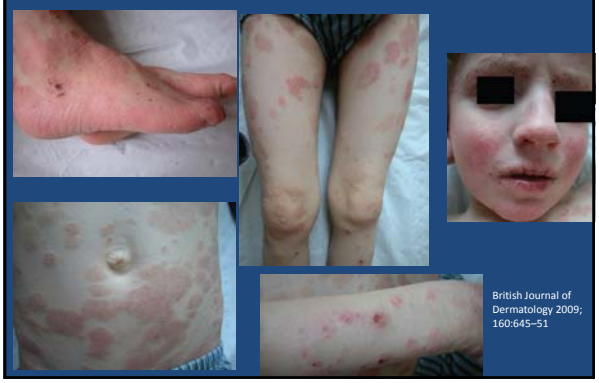


Duodenal biopsy: Pre-transplant

Duodenal biopsy: Post-transplant

N Engl J Med, 2001;344(23):1758

Atopic Dermatitis in IPEX Syndrome



British Journal of Dermatology 2009; 160:645–51

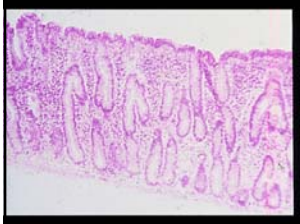
Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APCED)

- Major components:
  - Chronic mucocutaneous candidiasis
  - Hypoparathyroidism
  - Adrenocortical failure
- Range in presentation from 2 months to 20 years
- Only 5% of patients have diarrhea at presentation; about ¼ develop diarrhea by age 30.
- Hypocalcemia leads to significant diarrhea.
- Mutations found in AIRE gene that produces a cytoskeletal protein in the nucleus and cytoplasm.

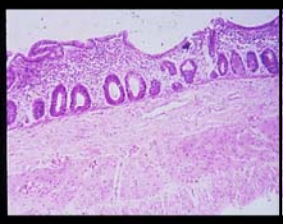
Biopsy features of autoimmune enteropathy (AIE)

- Severe enteropathy with marked villous blunting
- Intense lymphocytic (CD3+ T cells) lamina propria infiltrate
- Injured surface epithelial cells
- Crypt number may be decreased in AIE
- Intraepithelial lymphocytes NOT increased in AIE
- May see non-specific changes in the colon

Duodenal Biopsy



Autoimmune Enteropathy or Celiac Disease



Microvillous Inclusion Disease

What to look for

- Infection: viral, cryptosporidium, parasites
- Cow's milk/protein enteropathy (?RAST testing)
- Immunoregulatory defect
  - Quantitative immunoglobulins (G, A, M, E)
  - IgG subclasses
  - Anti-PRP and anti-tetanus antibody
- Neuroendocrine
  - VIP, gastrin, urine vanillylmandelic acid (VMA)

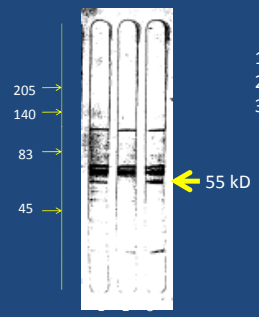
Diagnosis of autoimmune enteropathy

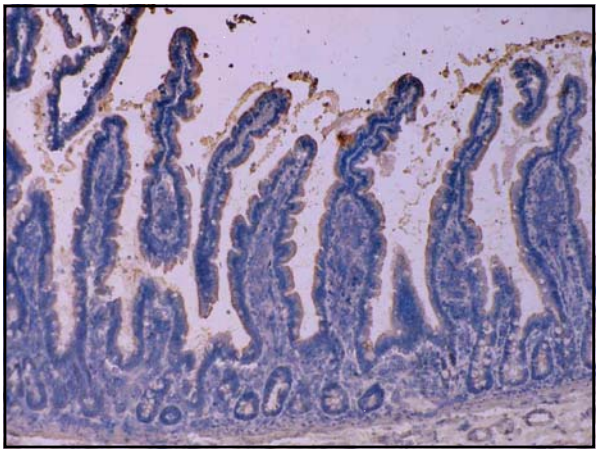
- Diagnosis is determined by having a positive IgG, IgA or IgM antibody directed against the enterocyte
- Is this specific for this disease?
- Is the presence of an anti-enterocyte antibody related to the mechanism of intestinal injury?
- Does the titer of the anti-enterocyte antibody correlate with the severity of epithelial injury?

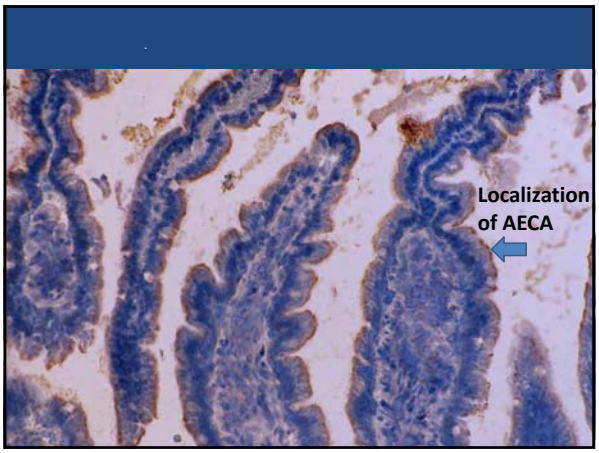
Diagnostic test

- Western Blot identifies an IgG or IgA antibody that reacts with a protein found in a homogenate of the small intestinal mucosa
- Immunohistochemistry localizes the IgG or IgA antibody to the surface of the enterocyte

Western Blot: Anti-enterocyte antibody







Treatments for Autoimmune Enteropathy

- Corticosteroids
- Azathioprine
- 6-Mercaptopurine
- Mycophenolate Mofetil
- High-Dose Cyclophosphamide
- Cyclosporine
- Tacrolimus
- Infliximab

What can we learn from these case reports of treatments?

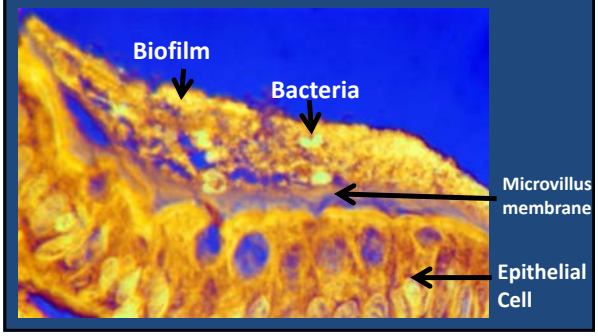
- Some patients respond to immunosuppression, but relapse when medications are tapered or stopped
- Prolonged use of low dose corticosteroids with or without an immunomodulator may be beneficial for many patients
- There do not appear to be predictors that can guide the decision to select the “best” agent for a specific patient
- Response to therapy does not always mean that the mucosa has healed

Remember

- Evaluate adaptive and innate immune function
- Infants with epithelial cell defects often present within the first two weeks of life
- Infants with autoimmune enteropathies usually have onset of symptoms after one month of age.
- Look for skin, renal, and endocrine involvement
- Intraepithelial lymphocytes NOT increased in AIE
- Treatment is trial and error

Intestinal Surface

Photograph by Dr. Cecil Fox, Little Rock, AR



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NASPGHAN Postgraduate Course 2010
Harland Winter, MD
October 21, 2010

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Ellis D et al. Familial occurrence of renal and intestinal disease associated with tissue autoantibodies. Am J Dis Child 1982;136:323-326.

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McCarthy DM et al. Selective IgA deficiency associated with total villous atrophy of the small intestine and an organ-specific anti-epithelial cell antibody. J Immunol 1978;120:932-938.

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Perheentupa J. Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy. J Clin Endocrinology & Metabolism 2006; 91(8):2843-50.

Savage MO, et al. Specific Autoantibodies to Gut Epithelium in Two Infants with Severe Protracted Diarrhoea. JPGN 4:187-195.

Unsworth J et al. Flat Small Intestinal Mucosa and Autoantibodies Against the Gut Epithelium. JPGN 1982;1:503-513.

Walker-Smith JA et al. Autoantibodies against gut epithelial in a child with small intestine enteropathy. Lancet 1982; 1:566-567.

Wang J, et al. Mutant Neurogenin-3 in Congenital Malabsorptive Diarrhea. N Engl J Med 2006;355:270-80.

Treatment:

Bousvaros A et al. Treatment of pediatric autoimmune enteropathy with Tacrolimus (FK506). Gastroenterology 1996;111:237-243.

Oliva-Hemker MM, et al. Remission of Severe Autoimmune Enteropathy After Treatment With High-Dose Cyclophosphamide. JPGN 2003;36:639-643.

Quiros-Tejeira RE, et al. Induction of Remission in a Child with Autoimmune Enteropathy Using Mycophenolate Mofetil. JPGN 2003;36:482-485.

Sanderson IR et al. Response to autoimmune enteropathy to cyclosporine A therapy. Gut 1991;32:1421-1425.

Seidman EG et al. Successful treatment of autoimmune enteropathy with cyclosporine. J Pediatr 1990;117:929-932

Steffen R et al. Autoimmune enteropathy in a pediatric patient: partial response to Tacrolimus therapy. Clin Pediatr (Phila) 1997;36:295-299.

Vanderhoof JA and Young RJ. Autoimmune Enteropathy in a Child: Response to Infliximab Therapy. JPGN 34:312-316.

General:

Hill SM et al. Autoimmune enteropathy and colitis: is there a generalized autoimmune gut disorder? Gut 1991;32:36-42.

Jenkins HR et al. Systemic vasculitis complicating infantile autoimmune enteropathy. Arch Dis Child 1994; 71:534-535.

Murch SM. Toward a Molecular Understanding of Complex Childhood Enteropathies. J Pediatric Gastroenterology and Nutrition 2002;34:S4-S10.

Russo PA et al. Autoimmune enteropathy. Pediatr Dev Pathol. 1999;2:65-71

References in bold are included in syllabus

Celiac Controversies: Am I managing my patient correctly?

Ivor Hill MD

Celiac Controversies

Am I managing my patient correctly?

Ivor D. Hill, MB, ChB, MD.
Wake Forest University
School of Medicine.

Celiac Controversies

Disclosure Statement.

I have the following financial relationship to disclose:

Astra-Zeneca - Consultant

No products or services produced by this company is relevant to my presentation.

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Celiac Controversies

Diagnosed
Vs.
Undiagnosed

Symptomatic
Vs.
Asymptomatic

Who to test?
Biopsies?
Gluten sensitivity?
Long term risks?
Compliance monitoring?

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Celiac Controversies

- Objectives
- Care of the Asymptomatic Individual
  - Additional testing?
  - Supplemental treatment?
- Treatment of Celiac Disease
  - Non dietary interventions?
- Dietary Compliance Monitoring
  - Best method?

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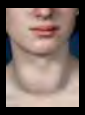
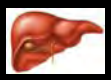
Celiac Controversies

- Care of the asymptomatic individual
  - Additional testing?

Bone health



Autoimmune



Liver - HBV

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Celiac Controversies

- Care of the asymptomatic individual

Bone health

Bone health assessment.
Dual energy X-ray absorptiometry (DEXA)
Quantitative computer tomography (QCT)
Ultrasonography
Metabolic markers of bone turnover

The problem!
Adults – at diagnosis
Osteoporosis ~ 28%
Osteopenia ?
Effect of a gluten free diet?

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Celiac Controversies

- Care of the asymptomatic individual

Recommendations

Bone health

Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease.
Gut 2000;46 (suppl 1):i1-i8.
American Gastroenterological Association Medical Position Statement: Guidelines on Osteoporosis in Gastrointestinal Diseases
Gastroenterology 2003;124:791-794

DEXA - at diagnosis
- after 1-2 years

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Celiac Controversies

- Care of the asymptomatic individual

What about children?
Problems with assessment
- changes more related to maturation

Bone mineral status at diagnosis
- Radial BMC and BMD lower in CD
- No relationship to clinical features
- Prevalence unknown (small "n")

Bone health

Effect of a gluten free diet on bone health
- complete resolution by 1 year
- maintained long term with compliance

Mora S. Rev Endocrin Metab Disord 2008;9:123-30

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Celiac Controversies

- Care of the asymptomatic individual

Recommendations in children*
- DEXA scans unnecessary
- institute a strict gluten free diet
- promote calcium & vitamin D
- monitor for dietary compliance

Bone health

* Gastroenterology 2003;124:791-794
* Mora S. Rev Endocrin Metab Disord 2008;9:123-30

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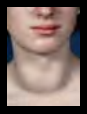
Celiac Controversies

- Care of the asymptomatic individual



Autoimmune (AI)

Associated conditions
- type 1 diabetes
- thyroiditis
- Addison's disease
- hepatitis

Question?
- screen those at risk for CD?
- screen those with CD for other AI diseases?

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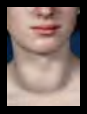
Celiac Controversies

- Care of the asymptomatic individual



Autoimmune

Autoimmune thyroiditis
- screen with anti-TPO & anti-Tg
- follow with TSH and free T4
- thyroid ultrasound

Prevalence of autoimmune thyroiditis in children with celiac disease and effect of gluten withdrawal.
J Pediatr 2009;155:51-5.
Long-term clinic significance of thyroid autoimmunity in children with celiac disease.
J Pediatr 2010;156:292-5.

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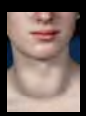
Celiac Controversies

- Care of the asymptomatic individual



Autoimmune

Thyroid autoimmunity in children with CD
- combined "n" of 425 children
- 25-30% positive antibodies (1/3 at diagnosis)
- 2-8% hypothyroid

Conclusions
- thyroid antibodies not related to gluten exposure
- thyroid antibodies do not predict thyroid hypofunction
- thyroiditis is not prevented by a GFD

Recommendations?
- screen for antibodies
- check positives for hypothyroidism

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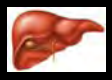
Celiac Controversies

- Care of the asymptomatic individual



Liver - HBV

The problem!

- non response to HBV vaccine linked to HLA DQ2
- ~50% of children with CD are non responders*
- more non responders in early onset CD#

*Park S-D et al. *J Pediatr Gastroenterol Nutr 2007;44:431-435*
*Noh KW et al. *Am J Gastroenterol 2003;98:2289-92*
#Leonardi S et al. *Vaccine 2009;27:6030-3*

Recommendations?

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Celiac Controversies

- Supplemental treatment in the asymptomatic?

Vitamins?

Minerals?

At diagnosis

- vitamin A,D, and B12 & folic acid
- iron, zinc, magnesium

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Celiac Controversies

- Supplemental treatment in the asymptomatic?

Vitamins?

Minerals?

Following recovery on a GFD?

Zinc

Zinc supplementation to patients with celiac disease – is it required? *J Trop Pediatr 2010 ; doi:10.1093/ tropej /fmq011*

Vitamin D – daily dose of 400 to 1000 IU per day

Medical Progress – Vitamin D Deficiency *NEJM 2007;357:266-81.*
Prevalence of D Deficiency in Children Report *Pediatrics2009;124:e362-e 370.*
- 9% deficient and 61% insufficient.
AAP Committee on Nutrition Report *Pediatrics 2006;117:578-85.*
AAP SoBr and CON Report *Pediatrics 2008;122:1142-52.*

Celiac Controversies

- Treatment of celiac disease

Role of steroids?

Role of pancreatic enzymes?

Is gluten free the only way?

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Celiac Controversies

- Treatment of celiac disease

Role of steroids?

Celiac crisis* – uncommon but potentially fatal!

- good evidence that steroids are beneficial

*Celiac crisis – severe diarrhea with dehydration and metabolic disturbance including decreased K^+, Ca^+, Mg^{++} and hypoproteinemia.

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Celiac Controversies

- Treatment of celiac disease

Role of pancreatic enzymes?

The problem!

- at diagnosis, enzyme insufficiency ~ 25%
- cause – malnutrition vs. gut regulatory peptides
- pancreatic function recovers following remission
- benefits of using enzyme therapy?

Carroccio A et al. *Gut 199132:796-99.*

Carroccio A et al. *Dig Dis Sci 1994;39:2235-42.*

Carroccio A et al. *Dig Dis Sci 1995;40:2555-60.*

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Celiac Controversies

- Treatment of celiac disease

Is gluten free the only way?

- Intraluminal approach
  - Modification of wheat protein
  - Transamidation of wheat flour (tTG + lysine methyl ester)
    Gastroenterology 2007;133:780-789
  - Digestive enzymes
    - Two prototypes (ALV003, *Aspergillus niger*)
    - Challenges? Gastroenterology 2005;129:786-796
  - Peptide binding agents
    - Challenges? Gastroenterology 2009;136:288-298

Celiac Controversies

- Treatment of celiac disease

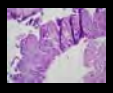
Is gluten free the only way?

- Biological antagonists
  - Zonulin inhibitor — Gastroenterology 2009;136:A-35
  - tTG inhibitors — Chem Biol 2005;12:469-475
  - DQ2 & DQ8 inhibitors — Proc Natl Acad Sci 2004;101:4175
  - Cytokine inhibitors — Gut 2005;54:46-53
- Novel therapies
  - Vaccine — Sci Translational Med 2010;2:1-14; J Immunol 2009;183:2390-2396

Challenges?

Celiac Controversies

- Dietary compliance monitoring
- Methods
  - Repeat biopsies



    - Gold standard
    - Feasibility?
  - Serological testing
    - How good are they?
    - Which tests are best?
  - Dietary review

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Celiac Controversies

- Dietary compliance monitoring
  - Serological testing

Dynamics of celiac disease-specific serology after initiation of a gluten free diet and use in the assessment of compliance with treatment.
Sugai E et al. Dig Liver Dis 2010;42:352-358

Conclusions:

1. tTG and EMA best.
2. Correlates with dietary review and repeat biopsies.

Five year time course of celiac disease serology during gluten free diet: results of a community based "CD-Watch" program.
Zanini B et al. Dig Liver Dis doi:10.1016/j.dld.2010.05.009

Conclusions:

1. Annual testing improves compliance from 82%-93%
2. Negative test indicates absence of major dietary transgressions

Celiac Controversies

- Dietary compliance monitoring
  - Dietary review – methods
    - Diet record analysis
    - Self administered questionnaire
    - Trained interviewer assessment
      - Low cost & strong correlation with biopsy*

A gluten free diet score to evaluate dietary compliance in patients with coeliac disease. *Brit J Nutr 2009;102:882-887*

Four questions based on strategies of gluten avoidance. Five level score (0-IV) Results compared to EMA and biopsy findings.

Scores distinguish those who are compliant!

*Arch Dis Child 1989;64:1604-1607.

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Celiac Controversies

- Conclusions
  - Asymptomatic cases
    - Screening

 X  √  ?

Bone health Autoimmune Liver - HBV

- Supplemental treatment

 X  √ for vitamin D

Minerals Vitamins

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Celiac Controversies

- Conclusions

Steroids — Celiac crises only

Pancreatic enzymes — No cost effective benefit

Gluten alternatives — Not ready for prime time – stay tuned!

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Celiac Controversies

- Conclusions
  - Dietary compliance monitoring
    - Repeat serology – tTG IgA
      - 3 mths ⟶ 6 mths ⟶ 12 mths ⟶ annually
  - Combined with:-
    - Dietary review
      - Nutritionist/Trained interviewer
      - Four question diet score?
    - Biopsies – select cases only

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Autoimmune Pancreatitis: My patient continues to have an elevated lipase and abdominal pain

Lee McHenry MD

Autoimmune Pancreatitis

NASPGHAN Conference

New Orleans, LA

Lee McHenry M.D.
Professor of Medicine
Indiana University

Disclosures

- Consultant for ConMed Endoscopic Technologies, Utica, New York
- *No Products or services produced by this company are relevant to my presentation.*

Goals and Objectives

- What is Autoimmune Pancreatitis (AIP) ?
- What is the pathogenesis of AIP ?
- Who does it affect ?
- How does AIP present ?
- How do I establish the diagnosis ?
- What is my approach to treatment ?

AIP
Definition

"A unique form of chronic pancreatitis characterized by swelling of the gland, irregular narrowing of the pancreatic duct, lymphoplasmacytic infiltration of pancreas, and favorable response to steroids"

AIP
Definition
(contd)

- Type I: lymphoplasmacytic sclerosing pancreatitis (LPSP)
- Type II: idiopathic duct centric pancreatitis

- Other organs may be affected
  - Cholangiopathy of extra and/or intrahepatic bile ducts
  - Kidneys
  - Retroperitoneum with fibrosis
  - Salivary glands
  - Lymph nodes
  - misc: prostate, aorta

AIP Historical Perspective

- **1961: Sarles**[1]
  - 1st description non-ETOH pancreatitis
    - Diffuse enlargement of pancreas
    - Marked lymphoplasmacytic infiltration
    - Elevated gammaglobulins
- **1995: Yoshida**[2]
  - proposed AIP as concept
- **1997: Ito**[3]
  - 3 cases AIP dramatic response to steroids
- **2001: Hamano**[4]
  - ⇑ **serum IgG 4 as marker**

[1] Sarles 1961 Am J Dig Dis 6:688, [2] Yoshida 1995 Dig Dis Sci 40:1561, [3] Ito 1997 Dig Dis Sci 42:1458,
[4] Hamano 2001 N Engl J Med;344:732

Pathogenesis

- Not well understood
  - ? Allergic ..... IgG-4 released in response to an antigen often occurs in allergic disorders
- Release cytokines ⟶ up-regulate HLA class II expression by duct epithelial cells ⟶ ab to CA II ag's (duct epithelium) and lactoferrin (acinar cells) ⟶ lymphocyte infiltration
- Animal models of AIP are in progress

AIP

- Who does it affect ?
  - older males > older females
  - Japan n = 40 Male 82% Age 61yrs (32-76)

	IU	UK	Mayo
n	20	11	29
age	50 (18-76)	53 (28-78)	63 (14-85)
male (%)	60	100	83

Kawa, Gastro 2002;122:1264 -9

Adult AIP
Clinical Presentation

- New onset jaundice (70%)
- Mild epigastric discomfort
- Weight loss

CT scan
- diffuse enlargement pancreas "Halo Sign"
- fluctuating pancreas masses

ERCP
- Diffuse or segmental narrowing of PD
- biliary stricture - distal or proximal

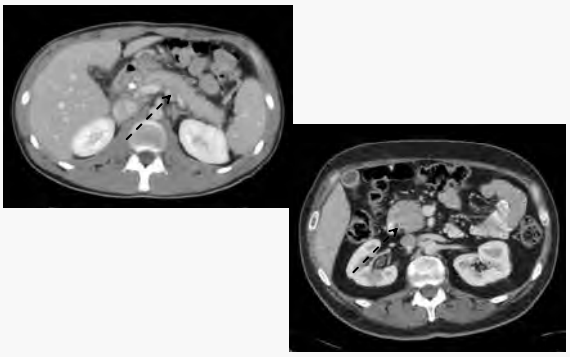
Pediatric GI Perspective AIP

- Few case reports
  - 11 y/o male, 14 y/o female, 16 y/o male
  - IgG 4 normal in all
  - Epigastric abd pain, enlarged pancreas, tissue from laparotomy, steroid responsive

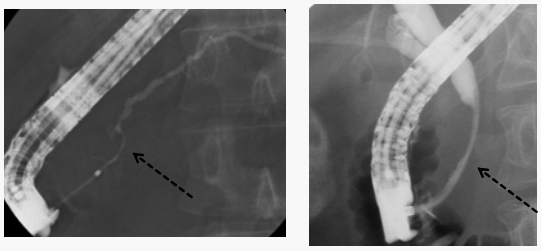
Age	N	Abd pain %	Amylase	jaundice
< 40 (28-37)	6	100	83	17
> 40 (42-78)	58	43	40	59
		p < 0.05	P < 0.05	NS

Bletjer, J Ped Surgery 2008;43:1368, Rafaat, Pediatr Radiol 2009;39:389, Takase, J Nippon Med Sch 2010;77:29, Kamisawa, J Clin Gastroenterol 2006;40:847

CT Scan in AIP



ERCP in AIP



Pancreatography in AIP

- Pancreatographic findings
  - ductocentric plasma cell infiltration of the pancreas
- Strictures may be segmental or diffuse
- Upstream dilation is minimal
- Ca++ is uncommon
- Cysts are uncommon

AIP
Making the Diagnosis

- For Research Purposes
  - Japan Criteria 2000
    - Revised 2006
  - Korean Criteria 2003
  - Mayo HISORt Criteria 2006
    - *H*istology, *I*maging, *S*erology, *O*ther organ involvement, *R*esponse to *t*herapy
- For Clinical Purposes
  - In the appropriate clinical setting
    - typical findings on ERCP +/- CT scan along with
    - supportive serology +/- histology

AIP Review Article
Mass General

Table 1. Diagnostic Criteria for Autoimmune Pancreatitis.*

Findings on Imaging Radiography (One Required)		Serologic and Histologic Findings (One Required)		
Cross-Sectional Imaging	ERCP or MRCP	Serologic Analysis	Pancreatic-Biliary Histologic Analysis	Nongastrointestinal Histologic Analysis
Diffusely enlarged pancreas	Segmental pancreatic ductal narrowing	Elevated serum IgG4 level	Periductal lymphoplasmacytic infiltration or fibrosis	Tubulointerstitial nephritis with immune deposits within tubular basement membranes
Enhanced peripheral rim of hypoattenuation "halo"	Focal pancreatic ductal narrowing	Elevated serum IgG or gamma globulin level	Obliterative phlebitis	Pulmonary interstitial lymphoplasmacytic infiltration with IgG4-positive plasma cells†
Low-attenuation mass in head of pancreas	Diffuse pancreatic ductal narrowing	Presence of ALA, ACA II, ASMA, or ANA	IgG4-positive plasma cells in tissue†	Chronic sialadenitis with IgG4-positive plasma cells†

Finkelberg, N Engl J Med 2006;355:2670-6

Diagnostic Yield in AIP Serology

- Autoantibodies in 10-100% pts with AIP
- 4 series from Japan/Korea

	%	n
ANA	39%	25/63
Lactoferrin	76%	16/21
ACA II	62%	13/21
RF	26%	10/36
AMA	4%	1/18
Antithryoglobulin	34%	14/41

Kim, Am J Gastroenterol 2004;99:1605

IgG 4 Serology Western Population

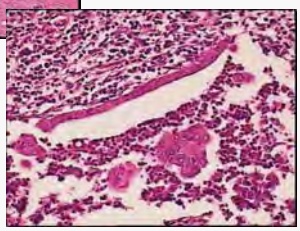
	IU	Florida	Spain	UK	Mayo
n	13	7	13	11	45
↑ IgG4	15%	28%	54%	63%	76%
Nl range (mg/dl)	1-291	1-210	1-130	1-164	8-140

Identification of a Novel Antibody associated with AIP

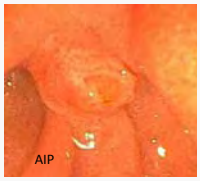
- N = 20 pooled serum samples with focal AIP
- library of dodecamer peptides screened with pooled serum samples
- Most promising peptide "AIP peptide"
  - 18 of 20 patients (90%) pathologically proven AIP
  - 4 of 40 pancreas cancer patients (10%),
  - 0% healthy controls, benign pancreas
- AIP peptide has homology to
  - PBP protein of H pylori and human UBR2 protein
  - independent AIP group 33 of 35 + PBP ab (94%)
  - pancreas cancer group 5 of 110 + PBP ab (5%)

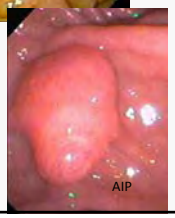
Frulloni L, N Engl J Med 2009 361:2135-42

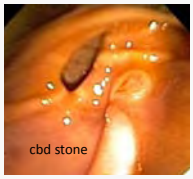
Plasma Cells



Papillas







Diagnostic Yield of Ampulla Biopsy

- IgG-4 Immunostaining > 10 / HPF

	AIP	Pancreas Ca	Papillitis	PSC
Diagnostic AIP[1]	8/10	0/10	0/10	-
Diagnostic AIP[2]	18/27	-	-	0/12

- All diagnostic specimens were in patients with head of pancreas involvement
- 2 negative ampulla bx – body and tail

1. Kamisawa, Gastrointest Endosc 2008:
2. Kubota, Gastrointest Endosc 2008;68:1204.

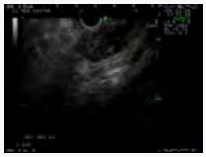
IgG-4 tissue immunostaining

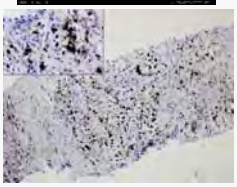
- Technique standardized
- Must be performed on tissue
  - no standard for cell block
- Many tissues including pancreas cancer have scarce IgG-4 staining plasma cells
- > 5 high-power fields examined
- Positive if: + IgG-4 plasma cells > 10 / HPF

Deheragoda, Clin Gas Hepatol 2007;5:1229

EUS in AIP - Tissue Acquisition

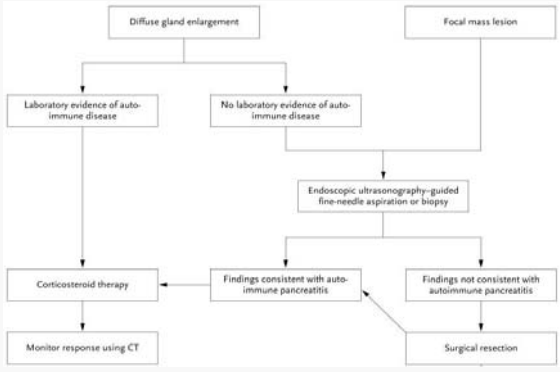
- EUS core biopsies
  - 7/16 (44%) diag histology
  - 15/16 (96%) diag IgG-4 immunostain
- Resection specimens
  - 12/13 (94%) diag histology
  - 13/13 (100%) diag IgG-4 immunostain





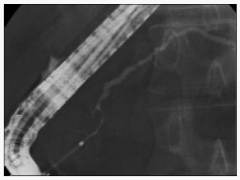
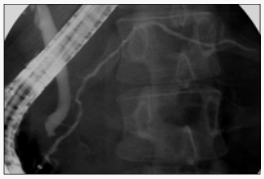
Chari, Clin Gast Hepatol 2006;4:1010

Treatment Algorithm



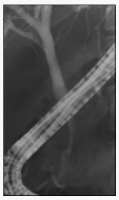
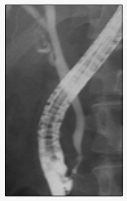
Steroids and AIP

- Steroid effect is dramatic
  - Clinically effective
  - Morphologically effective
  - Serologically effective
- Optimum dose/duration not fully established
- Relapse in approximately 1/3rd

Steroids and AIP

- Regimen
  - Begin: **Prednisone 30 – 40 mg/day x 4 wks**
- Follow-up at 1 month
  - If responding by CT or ERCP or symptoms
    - Taper: week 4, decrease 5 mg q 4 wk
- Follow-up at 5 months
  - Consider discontinuing steroids or maintenance 5-10 mg/day

Steroids and AIP

- Follow-up at 12 months
  - If relapse, reinstitute prednisone 40 mg/day and add azathioprine 1.5 mg/kg
    - IgG-4 associated cholangitis more likely to relapse (proximal > distal)
    - Systemic IgG-4 associated diseases
  - Cytoxan has been used
  - Rituximab has been used

AIP – Pearls about patients

- Pearls
  - In adults: older, male with jaundice, enlarged pancreas or mass . . . . be hyperaware, consider AIP
  - In pediatric patients:
    - epigastric pain, elevated amylase, enlarged pancreas,
    - IgG 4 unreliable, IgG4 stain diagnostic
- Procure Plasma cells from papilla or pancreas
- Pancreatography – segmental or diffuse strictures
- Prednisone – rapid response

Thank You !

Learning Objectives:

1. Define autoimmune pancreatitis (AIP) and understand how AIP differs from other pancreatic diseases.
2. Understand the clinical presentation of AIP in the adult and the pediatric population.
3. Know the diagnostic strategy for AIP and diagnostic criteria to establish the diagnosis.
4. Understand the long-term risks and treatment approach to AIP.

Syllabus

Introduction:

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis characterized by swelling of the gland, irregular narrowing of the pancreatic duct, lymphoplasmacytic diffuse infiltration of the pancreas, and favorable response to corticosteroids. This disease entity was first described by Henry Sarles in 1961 in select patients carrying the diagnosis of chronic pancreatitis with diffuse pancreatic enlargement and elevated serum immunoglobulins who had a dramatic response to steroids. It was in 1995 that Yoshida first proposed the term Autoimmune Pancreatitis as a concept. Over the past 15 years, further investigation of this uncommon cause of chronic pancreatitis has led to further classifying AIP into Type I AIP: lymphoplasmacytic sclerosing pancreatitis (systemic disease with IgG4 positive plasma cells infiltrating the pancreas and other organs) and Type II AIP: idiopathic duct centric pancreatitis (predominant granulocyte epithelial lesion surrounding the pancreatic duct). The two types vary in their clinical presentation, their pathologic findings and the long-term response to corticosteroids.

Epidemiology:

The true prevalence of autoimmune pancreatitis remains to be determined as most reports are case series by tertiary medical centers from around the world. In Japan, Nishimori conducted a nationwide study in 2002 and reported a prevalence rate of 0.82 AIP patients per 100 000. AIP has been reported to account for 5-6% of patients with idiopathic pancreatitis in Japan.

Pathogenesis

Autoimmune pancreatitis is an inflammatory disease of the pancreas with unique clinical and histologic features. The etiology of autoimmune pancreatitis may indeed be autoimmune, but to date it has not been proven. The overall pathogenesis of AIP is unclear, but appears to T helper type 2 cells and T regulatory cells mediate the immune reaction, and that mutations in HLA class II molecules of the host may predict high rates of relapse in Korean patients with AIP.

Serologic markers such as IgG-4, carbonic anhydrase, lactoferrin and antinuclear antibody have been detected in autoimmune pancreatitis patients, however, these markers are not organ-specific and lack the sensitivity/specificity to be considered a diagnostic marker for AIP. A recent report from Frulloni in Verona, Italy reported on a novel antibody 'peptide AIP' that was recognized by serum from 18 of 20 (90%) patients with autoimmune pancreatitis as compared to 4 of 40 patients (10%) with pancreas cancer. The peptide showed homology to the plasminogen-binding protein (PBP) of H pylori and with UBR2, an enzyme highly expressed in acinar cells of the pancreas. Antibodies against the PBP peptide was detected in 33 of 35 patients (94%) with AIP and 5 of 110 patients (5%) with pancreas cancer. Further investigation is warranted to validate these preliminary results before serum PBP could be considered a serologic marker for AIP.

Clinical Presentation and Diagnosis

Autoimmune pancreatitis is a male-predominant disease with a median age > 45 years. However, there are increasing number of case reports of 11 – 25 year old patients that present with AIP, and appear to present in a distinctive fashion (with more frequent abdominal pain, higher frequency of hyperamylasemia, and less likliehood of jaundice) as compared to the adult population. Diagnostic criteria (Korean 2003, Japan 2006, Mayo HISORt 2006) have been proposed based on clinical, radiologic, serologic, and histologic findings as well as the patient's response to corticosteroid therapy.

The 'classic' patient with autoimmune pancreatitis may be a 55 year old male with vague, nagging epigastric discomfort, mild hyperamylasemia, diffusely enlarged pancreas with "halo" sign on CT scan, narrowed and irregular pancreatic duct on ERCP or MRCP and elevated serum IgG 4 level. Institution of corticosteroids would rapidly improve symptoms, resolve the radiologic abnormalities and normalize the IgG 4 level. However, other clinical presentations of AIP may include patients who present with a focal pancreas mass suggestive of pancreas cancer, new onset jaundice with distal or proximal biliary strictures on imaging, and other organ involvement such as retroperitoneal fibrosis or hypodense renal lesions on CT imaging. The pathologic diagnosis of AIP can be established by biopsy of the pancreas, duodenal ampulla, bile duct, liver or other affected organs revealing IgG4 + plasma cells (>10/HPF) on histologic sectioning.

Management

Corticosteroids are the cornerstone of therapy for patients with autoimmune pancreatitis approaching 100% response in almost all series in the literature. The response is dramatic within the first 1-2 weeks of therapy and the prednisone is gradually tapered to 5-10 mg/day over 4-6 months. The optimum schedule for long-term steroid therapy has not been established. Relapses are not uncommon occurring in over 1/3 of patients. Immunosuppressants including azathioprine, cytoxan, and rituximab have been used to treat relapses in AIP patients. Further clarification of the most effective long-term treatment for paitents with autoimmune pancreatitis is anticipated as our understanding of the natural history of this condition continues to evolve.

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