Recent Advances in Autoimmune Gastrointestinal Disorders

Advances in Digestive Diseases 2019: Highlights from DDW
6/1/19
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Outline

• Celiac Disease
• Microscopic Colitis
• Autoimmune Hepatitis
• IBD
• EoE
• Autoimmune gastritis
• Autoimmune enteropathy
• PBC
• PSC
Outline

• Celiac Disease
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• Autoimmune Hepatitis
• IBD
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• Autoimmune enteropathy
• PBC
• PSC
Celiac Disease

it’s not me, it’s you.
Celiac Disease

- Immune mediated small intestine enteropathy
- Partial gluten digestion
- Bind HLA DQ on APCs
  - Activate CD4+ T cells
    - Proinflammatory cytokine
    - Stimulates B cell response
  - Promote IEL activation
    - Transform to NK like cells
    - Destroy enterocytes

Tye-Din JA et al. Front Pediat. 2018
Celiac Disease

• Injury $\rightarrow$ less absorptive area $\rightarrow$ reduction in digestive enzymes $\rightarrow$ micronutrient deficiencies
  – fat soluble vitamins, iron, B12, Folic acid

• Inflammation exacerbates malabsorption by causing secretion of fluid that increases diarrhea

• 100% of patients possess specific variants of HLA class II genes - HLA-DQ2 and DQ8
  – 90% DQ2
  – 20-30% of US population carry these genes—only 2-3% of these people will get CD

Lebwohol B et al. Lancet. 2018
Celiac Disease

• Presentation – Asymptomatic to severe malnutrition
  – GI – pain, bloating, diarrhea, dyspepsia, weight loss, steatorrhea
  – Extra-intestinal – fatigue, joint pain, cognitive impairment
• Signs – IDA, AST/ALT, micronutrient, opsteopenia
• Diagnosis – TTG IgA or deaminated Gliadin IgA/IgG
  – 10 g gluten x 6 weeks
  – If labs abnormal, pursue biopsy
  – Check total IgA – 2-5% are IgA deficient
  – False positive TTG – other autoimmune diseases (ie RA, psoriasis, hashimotos)
• Genetic testing can definitively rule out CD if patient doesn’t want EGD or won’t come of GFD
Celiac Disease

• Biopsy – 2 duodenal bulb, 4 D2 separate jars (histology can be patchy)

• Endoscopic findings in severe disease
  – Villous atrophy
  – Scalloping
  – Fissuring of mucosa
Celiac Disease Management

• GFD – avoid wheat, barley, rye , caution with oats
• Repeat serologies q3-6 mo
• No consensus on repeat EGD with biopsies
• Bone density, Pneumococcal/Flu vaccines, micronutrient deficiencies (vitamin A, D, E, K, B12, folate, copper, iron, zinc)
• Refractory disease
  – Confirm diagnosis
  – Type 1 – Better prognosis, treatment systemic steroids or immunosuppressive
  – Type 2 – Poor prognosis (high risk t cell lymphoma), may require TPN
Future Therapies

- Inactivation of the toxic peptides in the bowel lumen
- Prevention of passage of gliadin into the mucosa
- Induction of immune tolerance
- Inactivation of the immune process in the lamina propria
- Phase 2 studies
  - Larazotide acetate - oral peptide that modulates tight junctions and prevents passage of gliadin peptides through the epithelial barrier
  - Latiglutenase - enzyme preparation that prevents the pathological damage caused by gluten

Lebwohol B et al. Lancet. 2018
Incidence of Celiac Disease is Increasing Over Time: A Systematic Review and Meta-Analysis

- Female incidence 17.4 (95% CI: 13.7, 21.0) per 100,000 person-years,
  - compared to 7.8 (95% CI: 6.3, 9.3) in males
- Children 20.1 per 100,000 person-years (95% CI: 16.0, 24.3) compared 13.2 (95% CI: 8.6, 17.8) in adults.
- Low incidence until the 1990s and since then diagnoses started to substantially increase annually

King JA et al. DDW 2019, San Diego, CA. #2000
Real Life Patterns of Gluten Free Diet Adherence in Celiac Patients Using GIP Excretion

• Patients with CD are often exposed to gluten contamination
• Gluten immunogenic peptides (GIP) in stool and urine are very specific for gluten exposure

<table>
<thead>
<tr>
<th>Sample</th>
<th>Methods</th>
<th>Sensitivity/specificity</th>
<th>Time to excretion</th>
<th>Time to GIP clearance</th>
<th>Levels of gluten intake for detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool</td>
<td>ELISA/LFIA</td>
<td>100/100</td>
<td>2 days</td>
<td>2-5 days</td>
<td>&gt;50 mg/d</td>
</tr>
<tr>
<td>Urine</td>
<td>LFIA</td>
<td>99/100</td>
<td>1-6 hours</td>
<td>18-36 hours</td>
<td>&gt;50-500 mg/d</td>
</tr>
</tbody>
</table>

Stefanolo JP et al. DDW 2019, San Diego, CA. #596
Real Life Patterns of Gluten Free Diet Adherence in Celiac Patients Using GIP Excretion

- **Aim:** Explore GFD transgression in long term GFD pts (>2yr) using GIP
- **Methods:** Collect stool on Friday and Urine Sunday x 4 weeks
- **Results:** Interim analysis of n=23 (final n=53)
  - 95.6% excreted GIP at least one time in 4 week period
    - 91.3% had one positive urine GIP (weekend)
    - 47.8% had one positive stool GIP (weekday)
    - 44.6% of all urine tests were positive for GIP
    - 26.1% of all stool samples were positive for GIP
    - Significant difference between stool and urine (weekdays vs weekends)
      - Urine sample vs stool sample p < 0.02

Stefanolo JP et al. DDW 2019, San Diego, CA. #596
**Real Life Patterns of Gluten Free Diet Adherence in Celiac Patients Using GIP Excretion**

- Increase in number of positive tests as study progressed – significant difference between 1 and 4 — Hawthorne effect
- No difference between sx and asx patients
- No association between sx and GIP positivity
- Conclusions: High frequency of transgressions with CD on GFD, independent of presence of symptoms
- Gluten ingestion more frequent during weekends

Stefanolo JP et al. DDW 2019, San Diego, CA. #596
Effect of *Bifdobacterium infantis* NSL Super Strain in Highly Symptomatic Celiac Disease Patients

• 30-50% of CD patients have persistent or relapsing symptoms on GFD
• *B. infantis* alleviated symptoms in newly diagnosed patients with CD
  – Modulation of innate immunity
• Aim: 3 week course of *B. infantis* in symptomatic CD patients on GFD x 2 years
• Prospective, randomized, cross-over, double blind
• Outcomes: Celiac Symptom Index score, fecal microbiota, adverse events

Smecuol E et al. DDW 2019, San Diego, CA. #599
Pinto-Sanchez J Clin Gastro. 2017
Effect of *Bifidobacterium infantis* NSL Super Strain in Highly Symptomatic Celiac Disease Patients

- Results: $n = 12$, overall no change
- Patients with higher burden symptoms had improved Celiac Symptom Index, especially in CD specific symptoms
  - Trend for probiotic effect in general health score (not significant)
- Higher abundance of *Bifidobacterium* in probiotic group
- No adverse events
- Conclusion: *B infantis* may improve CD symptoms
Concordance of Bulb and Distal Duodenal Findings in Celiac Disease Follow up Biopsies

• Ongoing mucosal injury associated with complications
  – Malnutrition, osteoporosis, lymphoma
• At diagnosis guidelines advise sampling bulb and distal duodenum
• Aim: define concordance between bulb and distal duodenal biopsies in multinational cohort
  – 10 US and 3 European studies

Patel N et al. DDW 2019, San Diego, CA. #600
Concordance of Bulb and Distal Duodenal Findings in Celiac Disease Follow up Biopsies

• Results: n = 239, 478 biopsies from 2 time points
  – Mean interval follow up time 3.3 years
• 75% concordance at time point 1 and 87% at time point 2
• 12 patients with discordant findings at time 2 – bulb only
  – All had persistent symptoms and 2 persistent positive TTG serology
• Symptom profile, TTG and GFD do not predict villous blunting or IEL at time point 2
• Conclusions: 55% had persistent blunting or IEL
  – Minority have inflammation in the bulb only
  – Should consider follow up biopsies in the bulb as well

Patel N et al. DDW 2019, San Diego, CA. #600
Economic Burden of Celiac Disease in the U.S.

- Retrospective, observational 1:1 matched cohort study x 24 months
  - 11,008 CD vs 11,008 controls in medical claims database
- Aim: real world burden of CD
- All health care utilization
- 71.3% female, mean age 40.7 yo
- Inpatient admissions – 16.8% vs 13.4% (p < 0.0001)
- ER visits – 42% vs 35.6% (p < 0.0001)
- All cause cost - $34,536 vs $22,839
  - Driven mostly by outpatient services

Taylor A et al. DDW 2019, San Diego, CA. #649
An Acute Rise in Serum IL-2 But Not Symptoms Differentiates CD from NCGS

- GI and Non-GI complaints common after gluten exposure in Celiac Disease and Non-Celiac Gluten Sensitivity
- Sxs: Minutes – Hours after exposure
- IL-2 secreted by T cells as marker of adaptive immunity
- Aim: RCT double blind placebo controlled gluten challenge
  - Determine if subjects could accurately identify gluten exposure
  - Serum IL-2 in CD vs NCGS
- n = 20 in CD, NCGS, and Healthy
  - Given 6 g of gluten (equivalent to 2 slices of bread)
    - Regular flower vs Rice flower mixed with Tang to mask taste

Cartee A et al. DDW 2019, San Diego, CA. #825
An Acute Rise in Serum IL-2 But Not Symptoms Differentiates CD from NCGS

• CD – no difference in symptoms between gluten and placebo arms
  – Gluten - 8/10 subjects reported sxs– median 2.5 hrs
  – Placebo - 9/10 subjects reported sxx- median 1.5 hrs

• NCGS – also no difference
  – Gluten - 9/10 sxs– median 0.5 hours
  – Placebo - 9/10 sxs- median 1 hour

• HC – also no difference
  – Gluten - 6/10 HC sxs– median 5 hours
  – Placebo - 3/10 sxs– median 0.5 hours

• IL2 only increased in CD patients receiving gluten

Cartee A et al. DDW 2019, San Diego, CA. #825
An Acute Rise in Serum IL-2 But Not Symptoms Differentiates CD from NCGS

• Conclusions – gluten specific symptoms do not exist in CD, NCGS, and HC
  – Rapid IL2 response in CD patients - long term gluten specific T cell memory
  – T cell memory in GI tract remains despite “healed status”
  – Gluten specific T cells not involved in in NCGS
  – Cytokine response may have clinical utility in diagnosis CD in those on a gluten free diet

Cartee A et al. DDW 2019, San Diego, CA. #825
Benefits and Barriers of a Handheld Consumer Gluten Detector Among Adults and Teenagers with CD: A RCT

- Diminished QOL related to challenges of GFD
  - Dining out particularly hard

- Nima – commercially available portable gluten detector
  - Pea size sample of food detects gluten within 3 minutes
  - May detect samples of gluten so small that they are actually considered gluten free
    - Detects gluten < 20 parts per million
  - Not effective for beer, soy sauce, barley malt vinegar
Benefits and Barriers of a Handheld Consumer Gluten Detector Among Adults and Teenagers with CD: A RCT

Additionally: $5 for single use capsule

Wolf RL et al. DDW 2019, San Diego, CA. #823
Benefits and Barriers of a Handheld Consumer Gluten Detector Among Adults and Teenagers with CD: A RCT

- 3 month RCT with biopsy proven CD without Nima
- 83 teenagers and adults responded to flyers and emails
  - 18 adults and 65 teenagers
- Not instructed how to use Nima
- Results – Adults Improved CD-QOL score post NIMA- 45.7 vs 54.5 (p 0.005)
  - Fewer limitations related to eating out, socializing, traveling
  - No change in dietary adherence
  - Reduced depression scores – 15.3 vs 11.3 (p 0.03)
- No significant changes in any outcomes for teenagers
- Most would continue using it and recommend it to others with CD

Wolf RL et al. DDW 2019, San Diego, CA. #823
Microscopic Colitis

- Normal mucosa of colon:
  - epithelium
  - crypt

- Collagenous Colitis:
  - collagen

- Lymphocytic Colitis:
  - lymphocytes
Microscopic Colitis

- 2 main subtypes – similar clinically and epidemiologically
  - Collagenous colitis
  - Lymphocytic colitis
- Present with mild watery diarrhea, abdominal pain, mild weight loss, arthralgias
  - If severe weight loss, think alternatives
- Endoscopically normal
  - Histology > 20 IEL per 100 surface epithelial cells
  - IEL less prominent in CC
- Commonly have other autoimmune disorders
  - Up to 4.3% of patients with Celiac have MC
  - Celiac disease present in 2-9% patients with MC

Pardi DS. Am J Gastro. 2017
Microscopic Colitis

- Treat mild cases with dietary modification or antidiarrheal
- Bismuth if not effective
  - 53% response, 28% partial response
- Others use cholestyramine or mesalamine

Pardi DS. Am J Gastro. 2017
Microscopic Colitis

• Budesonide highly efficacious for induction
  – 4 RCTs – 4 collagenous colitis and 2 lymphocytic
  – 9 mg / day x 6-8 weeks +/- taper
  – Response 57-100% (~85%) vs 12-40%
  – Relapse ~ 80%

Bert, Gastro 2002
Miehlke, Gastro 2002
Bonderup, Gut 2003
Miehlke, Gastro 2009
Pardi, Gastro 2009
Miehlke, Gastro 2009
Microscopic Colitis

- Prednisone may be less effective
- Retrospective 80 pt trial – 50% LC 50% CC
- 21% treated with prednisone
- Remission 83% budesonide vs 53% prednisone (p 0.02)
  - But retrospective - may be biased
Microscopic Colitis

- MMX budesonide
  - Small trial data
  - N = 12 (1\textsuperscript{st} line in 8, 2\textsuperscript{nd} line 4)
  - 62.5\% Complete response 1\textsuperscript{st} line
  - 50\% response in second line
  - No AEs reported

Kamboj. Inflamm Bowel Disease. 2017
Treatment of Microscopic Colitis: When Steroids Fail

• Recurrence 70%
• It’s the minority that don’t recur
• Prolonged steroid reduce relapse but not to zero

Pardi DS et al. DDW 2019, San Diego, CA. #3455
Treatment of Microscopic Colitis: When Steroids Fail

• Wrong diagnosis?
  – IBS
  – IBD (review with exert GI pathologist)
  – Celiac disease
  – Drug induced Colitis
    • Less likely if patient has been on drug > 1 year
  – Concomitant diagnosis – SIBO, pancreatic insufficiency
  – Non compliance

<table>
<thead>
<tr>
<th>Drug (class)</th>
<th>Likelihood</th>
</tr>
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<tbody>
<tr>
<td>Acarbose</td>
<td>High</td>
</tr>
<tr>
<td>Aspirin</td>
<td>High</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>High</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>High</td>
</tr>
<tr>
<td>H2 receptor antagonists</td>
<td>High</td>
</tr>
<tr>
<td>SSRIs</td>
<td>High</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>High</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Flutamide</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Levodopa/benomazide</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Statins</td>
<td>Intermediate</td>
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</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drug; SSR1, selective serotonin reuptake inhibitor. Likelihood refers to the strength of data. Adapted from Beaugerie and Pardi (32).

Pardi DS et al. DDW 2019, San Diego, CA. #3455
Pardi DS. Am J Gastro. 2017
Treatment of Microscopic Colitis: When Steroids Fail

• Azathioprine
  – 8 out 9 patients in one study responded
  – Separate study n = 63, complete response 43%

• Methotrexate
  – 74% received some benefit but limited by side effects

• Anti TNF – infliximab and adalimumab
  – 8 INF, 2 ADA x 2-23 months – complete response in 4
  – Separate study n = 4 – all response with one dose, 2 switched to ADA, 3 in remission x 1 year

• Vedolizumab
  – n = 11, remission 45% after 3 infusions
  – 60% maintained remission

Pardi DS et al. DDW 2019, San Diego, CA. #3455
Pardi DS. Am J Gastro. 2017
Mortality in Microscopic Colitis: A Nationwide Cohort Study

- Swiss GI specific database 1965-2017
  - ICD 7-10
  - Controls matched by age, size, location
  - 69,489 controls vs 14,520 MC (4,655 CC and 9,965 LC)
- 20% higher risk of death for microscopic colitis
  - 30% increase risk of death if had disease > 10 years
  - 3% increase in absolute risk of death at 20 years
- No increase in cancer related death
  - CV, GI, and Infection related deaths were higher

<table>
<thead>
<tr>
<th></th>
<th>General Population Controls</th>
<th>Microscopic colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>12536</td>
<td>3628</td>
</tr>
<tr>
<td>Incidence Rate/1000 person-years</td>
<td>23.0</td>
<td>27.1</td>
</tr>
<tr>
<td>Age-adjusted HR (95% CI)</td>
<td>1.00</td>
<td>1.2 [1.1-1.2]</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>1.00</td>
<td>1.2 [1.1-1.2]</td>
</tr>
</tbody>
</table>

Khalili H et al. DDW 2019, San Diego, CA. #4140
MC pathogenesis may be related to inappropriate immune response to gut microbiota in those genetically susceptible

Analyzed microbiome of stool samples in 20 patients with MC vs controls

No significant difference in alpha diversity

Lower beta diversity in HC vs MC

Higher *Alistipes finegoldii* species in MC

In multivariate analysis higher *Haemophilus parainfluenza, Veillonella parvula* and *Veillonella unclassified* in MC

Lower *Alistipes putrredinis* in MC
  – Malnutrition, osteoporosis, lymphoma

Conclusion: microbiome may serve as biomarker (specifically *Alistipes putrredinis*)
Autoimmune Hepatitis
Autoimmune Hepatitis

- Chronic hepatocellular injury of unclear etiology
- Biopsy – Lymphocytic or lymphoplasmocytic infiltrate with interface hepatitis
- Incidence: 1.9 cases per 100,000 persons per yr
- Females account for 70% of cases, 50% ≤ 40 years
- AIH accounts for 2.6% and 5.9% of liver transplants in Europe and U.S. respectively

Prevalence of Autoimmune Hepatitis in the U.S. From 2013-2018: Population Based National Study

- Aggregate of Electronic Health Record data from 26 major integrated healthcare systems in the US
- 38,233,220 individuals and 11,580 individuals with AIH
- Overall prevalence rate of 30.3/100,000

Tunio NA et al. DDW 2019, San Diego, CA. #765
Autoimmune Hepatitis

- AIH can progress to cirrhosis, ESLD and death if untreated
- Steroids +/- AZA are standard treatment
  - 20% of patients don’t respond or tolerate
  - No established rescue therapy – options include budesonide, mycophenolate, tacrolimus, MTX

Agents equally effective in prior responders, but tacrolimus was superior in prior non-responders

Second Line Therapy for AIH

Roberts SK et al. Clinical Gastroenterol and Hepatol. 2018; 268-177
Readmissions in Hospitalized Patients with Autoimmune Hepatitis in Nationwide Inpatient Setting

- Retrospective cohort study using the 2014 Nationwide Readmissions Database
- Analyzed non-elective hospitalizations for AIH patients
- All cause 90 day AIH readmission rate 25.2%
  - hepatic encephalopathy, AIH, unspecified septicemia, non-alcohol-related cirrhosis, acute kidney failure
- AIH with cirrhosis had readmission rate 31.1%
- Multivariate analysis
  - Medicaid (OR 2.24; 1.53-3.26) and Medicare (1.54; 1.20-1.98) with private insurance as reference
  - Higher Charlson Comorbidity Index (1.13; 1.08-1.19)
  - Liver biopsy (0.69; 0.51-0.94) was associated with lower odds of readmission
    - Tissue diagnosis may trigger more appropriate therapy

Fan X et al. DDW 2019, San Diego, CA. #1528
Drug-Induced Autoimmune Hepatitis Caused by Infliximab: Clinical Features and Comparison with Patients with AIH

- Retrospective review of Icelandic patients with drug induced AIH (DIAH) vs AIH
  - 26 cases of DIAH between 2010-2018 from Infliximab
    - 45% rheum, 45% derm, 10% IBD
    - Median 4 infusions before abnormal liver tests
  - 58 patients with AIH
  - Median age DIAH 49 yo vs AIH 58 yo
  - Female: 80% DIAH, 86% AIH
  - Jaundice: 20% DIAH 41% AIH

Patel N et al. DDW 2019, San Diego, CA. #600
Drug-Induced Autoimmune Hepatitis Caused by Infliximab: Clinical Features and Comparison with Patients with AIH

• ALT similar in both groups
• Alk Phos lower DIAH (122 vs 207, p 0.03)
• IgG lower in DIAH (12 g/L vs 19 g/L, p 0.005)
• ASMA positivity lower in DIAH (5% vs 53% p < 0.05)
• 20% DIAH patients resolved spontaneously, 80% required immunosuppression
  – No relapses with median follow up 2.3 years
  – 55% given another TNF (adalimumab in 25% and etanercept in 30%) with no liver injury
• Conclusion: DIAH lower ASMA and IgG levels than AIH
  – 80% required immunosuppression, but no relapses and other TNF well tolerated

Patel N et al. DDW 2019, San Diego, CA. #600
Take Home Points

• Incidence of CD increasing over time
• > 90% GFD patients have some gluten as measured by GIP
• *B. infantis* may improve CD symptoms
• During follow up EGD for CD perform duodenal bulb biopsies
• Rapid IL-2 rise can differentiate CD for NCGS
• Gluten detectors don’t make teenagers happy, but may be good for adults
• Budesonide very effective for MC, but relapse common
• 20% higher risk mortality in MC patients
• Microbiome may serve as a marker for MC
• Liver biopsy for AIH may reduce readmissions
• Infliximab hepatitis has lower IgG and ASMA compared to AIH, and patients tolerate other TNF
THANK YOU
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6/1/19
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