ACG Hepatology Circle

Presents
Special Edition Virtual Grand Rounds
June 7, 2022 8:00 pm – 9:00 pm, EDT

Alcohol Associated Liver Disease

David E. Bernstein, MD, MACG  Jorge L. Herrera, MD, MACG  Suthat Liangpunsakul, MD, MPH, FACP

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- Colon
- Colorectal Cancer Prevention
- Endoscopy Video Forum
- Esophagus
- Functional Bowel Disease
- General Endoscopy
- GI Bleeding
- IBD
- Interventional Endoscopy
- Liver
- Obesity
- Pediatrics
- Practice Management
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- Stomach
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All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.
MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
 THESE ANSWERS WILL BE REVIEWED.

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Philip O. Katz, MD, MACG
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Week 23 – June 9, 2022
Overcoming the Challenges & Mitigating the Disparities in Our LGBTQI+ Patients: A Digestive Diseases Health Perspective
Sonali Paul, MD, MS
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Disclosures

Laura E. Raffals, MD, MS, FACP
Janssen Pharmaceuticals: Advisory Board

Edward L. Barnes, MD, MPH
AbbVie: Consultant
Gilead: Consultant
Pfizer: Consultant
Lilly: Consultant
Target RWE: Consultant

*All of the relevant financial relationships listed for these individuals have been mitigated

Off Label Discussion: Use of anti-TNF therapy, vedolizumab, ustekinumab for pouchitis
Pouch Dysfunction: Management Strategies for a Challenging Problem

Laura E. Raffals, MD, MS, FACG

OBJECTIVES

1. Describe normal pouch function
2. Review diagnostic approach to pouch disorders
3. Describe treatment of pouchitis
The anatomy of the pouch


Quinn KP, Faubion WA, Raffals LE. Inflamm Bowel Dis. 2019;460-471.
Normal Pouch Function

- 4-8 soft bowel movements a day, 1 nocturnal bowel movement
- No urgency
- No fecal leakage
- QOL measures improve 2-5 years after IPAA (University of Chicago & Cleveland Clinic)

QOL = quality of life; IPAA = ileal pouch-anal anastomosis.

How do we objectively define normal pouch function?

- First study of ano-pouch manometry and MR defecography in asymptomatic patients with anatomically normal pouch

25 patients with IPAA and self-reported healthy pouch function

25 patients completed HR-ARM + BET

20 patients completed MRD

14 patients included in analysis of normal pouch function

4 unable to return for MRD
1 contraindication to MRD
3 excluded by Rome Questionnaire
3 excluded by abnormal MDR
1 excluded by Rome Questionnaire + abnormal MDR

Flow chart of participant selection and inclusion process.

Quinn K, et al. Aliment Pharmacol Ther. 2022;00:1-9
Structural & functional abnormalities common among patients with self-reported ‘healthy’ pouch function

- Structural and/or functional pouch abnormalities identified in 30% (6/20) of subjects with self-reported healthy pouch function.
- 7 subjects had cuffitis or pouch wall thickening of > 4mm

• Figure: Intersphincteric perianal fistula (arrow, A and B) in an asymptomatic patient with IPAA identified during MR defecography.

Normal parameters proposed for high-resolution ano-pouch manometry, time to balloon expulsion, pouch barostat, and MR defecography in patients with an IPAA

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=14)</th>
<th>Women (n=6)</th>
<th>Men (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal resting pressure (mmHg)</td>
<td>72 ± 16</td>
<td>54, 97</td>
<td>73 ± 7</td>
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<tr>
<td>Anal squeeze pressure (mmHg)</td>
<td>247 ± 69</td>
<td>156, 369</td>
<td>223 ± 28</td>
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<td>Simulated Evacuation</td>
<td></td>
<td></td>
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<tr>
<td>Pouch pressure (mmHg)</td>
<td>44 ± 21</td>
<td>17, 79</td>
<td>31 ± 7</td>
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<td>Anal pressure (mmHg)</td>
<td>71 ± 43</td>
<td>29, 152</td>
<td>71 ± 18</td>
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<tr>
<td>Percent anal relaxation (%)</td>
<td>36 ± 21</td>
<td>8, 68</td>
<td>24 ± 8</td>
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<tr>
<td>Pouch-anal gradient (mmHg)</td>
<td>-27 ± 37</td>
<td>-86, 19</td>
<td>-40 ± 15</td>
</tr>
<tr>
<td>Balloon expulsion time (seconds)</td>
<td>54 ± 52</td>
<td>4, 120</td>
<td>74 ± 21</td>
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<td></td>
<td></td>
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<tr>
<td>First sensation (mL)</td>
<td>7 ± 4</td>
<td>2, 12</td>
<td>8 ± 2</td>
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<tr>
<td>Urge to defecate (mL)</td>
<td>19 ± 10</td>
<td>6, 33</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>Discomfort (mL)</td>
<td>30 ± 12</td>
<td>12, 46</td>
<td>33 ± 5</td>
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American College of Gastroenterology
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Ileal Pouch Syndrome (IPS)
the PROPS study

Symptoms
- Fecal Incontinence
- Soiling
- Urgency
- Frequency
- Clustering & Fragmentation
- Uncomfortable perianal symptoms
- Nocturnal symptoms

Consequences
- Pad Usage
- Toilet awareness
- Dietary and medical adjustments
- Alterations in sleep and energy
- Negative impact on intimacy
- Alterations in social roles
- Negative mental, emotional and psychological alterations

IPS diagnosis if at least one symptom and one consequence
IPS can be mild, moderate or severe
Pouchitis is most common cause of poor pouch function – but NOT only cause

Symptoms
• Fecal Incontinence
• Soiling
• Urgency
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IPS diagnosis if at least one symptom and one consequence
IPS can be mild, moderate or severe

Evaluating Pouch Complications

• Symptoms drive evaluation plan
  • Stool studies
  • Pouchoscopy
  • Enterography
  • MRI pelvis
  • Defecography
  • ARM

MRI = magnetic resonance imaging; ARM = anorectal manometry.
Pouch Complications

**Inflammatory/Infectious**
- Pouchitis
- Crohn’s
- Cuffitis

**Surgical/Mechanical**
- Leak
- Abscess
- Sinus
- Fistula
- Stricture
- SBO
- Prolapse

**Functional**
- Dyssynergic defecation
- Irritable pouch syndrome

**Dysplasia/Neoplasia**
- Dysplasia or cancer of pouch
- Dysplasia or cancer of anal transition zone

*SBO = small bowel obstruction.*

---

**Pouch Microbiota/Dysbiosis**
- ↑ Anaerobe:aerobe
- ↑ Strict anaerobes
- ↑ Clostridium species
- ↑ Sulfate reducing bacteria

**Immune Response**
- IL-1ra
- NOD2/CARD15

**Genetic Susceptibility**
- Extensive UC
- Backwash ileitis
- PSC/other EIMs
- Nonsmoking status
- NSAIDs

**Individual Risk Factors**
- Extensive UC
- Backwash ileitis
- PSC/other EIMs
- Nonsmoking status
- NSAIDs

*UC = ulcerative colitis; PSC = primary sclerosing cholangitis; EIMs = extraintestinal manifestations.*
Pouchitis

- **Idiopathic (most common - ~50-60%)**
  - Recurrence is common

- **Secondary Pouchitis**
  - Crohn's disease of the pouch
  - Infections (C. diff, CMV, etc.)
  - Ischemia
  - Medications/NSAIDs
  - Pouch evacuation disorder
    - Anastomotic strictures
    - Dyssynergic defecation

CMV = cytomegalovirus; NSAIDs = nonsteroidal anti-inflammatory drugs
Diagnosis

- Symptoms are **nonspecific**
- Severity of symptoms does **NOT** correlate with endoscopic and histologic inflammation

Classification of Pouchitis

- Duration of symptoms
  - Acute: <4 wk
  - Chronic: ≥ 4wk
- Response to antibiotic therapy
  - Antibiotic-responsive
  - Antibiotic-dependent
  - Antibiotic-refractory
**PATTERNS OF INFLAMMATION**

- Classic pouchitis
- PSC-associated pouchitis
- Ischemia

**POUCH INFLAMMATION**

Special considerations

- PSC
- Cuffitis
PSC-associated pouchitis

- Pouchitis is more common in patients with PSC
  - 1057 patients s/p IPAA for UC (54 w/ PSC)
    - 10-year cumulative pouchitis risk **79% PSC** vs **46% non-PSC**
- Frequently associated with pre-pouch ileitis
  - (53.8% PSC vs 17.6% non-PSC, p < 0.001)
- Inflammation more likely to be moderate to severe compared to UC-pouchitis
  - (54.9% vs 32.4%, p<0.001)

Quinn K, et al. *Clin Gastroenterol & Hepatol* 2021

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**PSC-Associated Pouchitis: A distinct phenotype**

All patients with PSC (n=9,743)

Patients with PSC and IPAA (n=357)

Patients with PSC and IPAA (n=225)

PSC-Pouchitis Cohort (n=162)

UC-Pouchitis Matched Cohort (n=162)

47 excluded for no pouchitis

62 excluded for PSC diagnosed after 1st pouchitis episode or unknown date of 1st pouchitis
42 excluded for Crohn’s disease of the pouch
20 excluded for no pouchoscopy on record
4 excluded for no follow-up

PAA, ileal pouch-anal anastomosis; PSC, primary sclerosing cholangitis

Quinn K, et al. *Clin Gastroenterol & Hepatol* 2021
### Pouchitis characteristics

<table>
<thead>
<tr>
<th></th>
<th>PSC-pouchitis (N=182)</th>
<th>UC-pouchitis (N=182)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at first pouchitis diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>41.4 ± 14.2</td>
<td>41.6 ± 13.3</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Pouchitis duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>58 (31.9%)</td>
<td>120 (65.9%)</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>124 (68.1%)</td>
<td>62 (34.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pouchitis severity at index pouchoscopy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (0.6%)</td>
<td>27 (14.8%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>83 (45.6%)</td>
<td>96 (52.8%)</td>
<td></td>
</tr>
<tr>
<td>Moderate-to-severe</td>
<td>98 (54.9%)</td>
<td>59 (32.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Prepouch ileitis at index pouchoscopy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>177</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pouchitis</td>
<td>6 (3.4%)</td>
<td>3 (1.8%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Chronic pouchitis</td>
<td>170 (94.1%)</td>
<td>158 (96.9%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (0.6%)</td>
<td>2 (1.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pouch dysplasia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3 (1.6%)</td>
<td>1 (0.5%)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Cuffitis</strong></td>
<td>27 (14.8%)</td>
<td>33 (18.1%)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Anastomotic stricture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>31 (17.1%)</td>
<td>36 (19.8%)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>C. diff pouchitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10 (4.4%)</td>
<td>7 (3.9%)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>CMV pouchitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

C. diff, Clostridioides difficile; CMV, cytomegalovirus; PSC, primary sclerosing cholangitis; SD, standard deviation; UC, ulcerative colitis

*Acute pouchitis: <4 pouchitis episodes per year, active pouchitis symptoms lasting <4 weeks, and responsive to a 2-4 week course of antibiotics; chronic pouchitis: ≥4 pouchitis episodes per year, active pouchitis symptoms lasting >4 weeks despite antibiotic treatment, or the requirement of chronic antibiotic or immunosuppressive therapy to control pouchitis symptoms.
### Multivariate analysis of the effect of PSC on pouchitis outcomes

<table>
<thead>
<tr>
<th>Pouchitis Outcome</th>
<th>Unadjusted OR</th>
<th>p value</th>
<th>Adjusted OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for ≥1 subsequent antibiotic course</td>
<td>4.10 (1.90, 8.87)</td>
<td>&lt;0.001</td>
<td>4.04 (1.52, 10.70)</td>
<td>0.005</td>
</tr>
<tr>
<td>Chronic antibiotic-dependent or antibiotic-refractory pouchitis</td>
<td>4.24 (2.74, 6.57)</td>
<td>&lt;0.001</td>
<td>4.71 (2.62, 8.47)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OR, odds ratio; PSC, primary sclerosing cholangitis

- Optimal treatment and treatment outcomes remain unclear
- Does bile acid composition in PSC patients differ from non-PSC chronic pouchitis?
Cuffitis

- Inflammation of rectal cuff
- **Urgency, tenesmus, blood** in the stool
- Small volume stools
- May respond to mesalamine suppositories

Pouch evacuation disorders

- Nerve damage
- Structural abnormalities
  - Ileoanal anastomotic stricture
  - Pouch prolapse at pouch outlet
  - Polyps in distal pouch
- Inadequate anal relaxation
- Paradoxical anal contraction
- Impaired pouch contraction (large pouch, decreased compliance)
- **Patients with chronic pouchitis more likely to have dyssynergic defecation**

Quinn et al. Clinical Gastroenterology and Hepatology; 2017. Vol 15;8
Treatment

Pouchitis treatment approach

- Ciprofloxacin 500 mg BID or metronidazole 500 mg BID x 2 weeks
- Repeat antibiotics PRN
- Antibiotic responsive
- Antibiotic maintenance
- Probiotics
- Consider antibiotic sparing strategies
- Antibiotic dependent
Pouchitis – Additional considerations

- If recurrence < 3 months, 2 weeks of antibiotic followed by tapered dose x 2 weeks

Antibiotic resistant intestinal microbiome predominant in antibiotic responsive pouchitis

- Prospective study aimed to explore microbial factors associated with response to antibiotic treatment of pouchitis
- Patients who develop pouchitis after J pouch surgery have less diverse microbiota compared to control
- Antibiotic treatment results in
  - ↓ pro-inflammatory microbiome
  - ↑ fluroquinolone resistance

Pouchitis – additional considerations

**Antibiotic Dependent**
- Should we consider *antibiotic-sparing* strategies?
  - Diet-based intervention
  - Super-probiotics/prebiotics
  - Biologics/Immunomodulators

Antibiotic refractory pouchitis

Rule out secondary causes of pouchitis (CMV, C diff, pouch evacuation disorder)

Is this surgical/mechanical complication?

Is this Crohn’s or Crohn’s like behavior of pouch?
Treatment options for antibiotic refractory pouchitis

- Vancomycin?
- Budesonide
- Immunomodulators
- Anti-TNF therapy
- Vedolizumab
- Ustekinumab
- Small molecules
- Surgery

AntitNFs for refractory pouchitis & CD-like pouch complications

<table>
<thead>
<tr>
<th>Disease</th>
<th>Short-term clinical remission (median 8 weeks)</th>
<th>Long-term clinical remission (median 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic refractory pouchitis</td>
<td>0.10 (95% CI 0.00-0.35; I^2=0.00)</td>
<td>0.37 (95 CI 0.14-0.62; I^2=0.047)</td>
</tr>
<tr>
<td>CD-like complications (Significant prepouch ileitis, non-anastomotic fistula, non-anastomotic stricture)</td>
<td>0.64 (95% CI 0.48-0.78; I^2=0.24)</td>
<td>0.57 (95% CI 0.43-0.71; I^2=0.32)</td>
</tr>
<tr>
<td>Inflammatory complications of pouch (Combining both refractory pouchitis &amp; CD-like complications)</td>
<td>0.50 (95% CI 0.37-0.63; I^2=0.57)</td>
<td>0.52 (95% CI 0.39-0.65; I^2=0.59)</td>
</tr>
</tbody>
</table>

Vedolizumab for refractory pouchitis


Vedolizumab – EARNEST trial – VDZ vs PBO + 4-week cipro

- 102 patients treated (51 per group)
- VDZ showed treatment benefits over PBO across clinical, endoscopic and histologic endpoints

Travis, S, et al. Vedolizumab intravenous is effective across multiple treatment targets in chronic pouchitis: Results of the randomized, double-blind, placebo-controlled EARNEST trial. ECCO, OP04 2021
Ustekinumab for CARP

- 24 patients
  - 50% previously failed anti-TNF and/or vedolizumab
  - PGA, Endoscopy PDAI, Change in # BMs
- 50% response per PGA
- Median change in BM -8 to 6/day (p=.002)
- Median change in endoscopic PDAI 5 > 4 (p=0.0.16)


Ustekinumab for chronic pouchitis & Crohn's Disease of the pouch

- Multicenter study of 56 patients treated with ustekinumab
- 65% failed anti-TNF and 38% failed VDZ after IPAA
- At 3 months, (n=43), 84% with clinical response
- At 6 months, (=42), 83% with clinical response
- At 6 months, (n=20), 60% had endoscopic response

Diet and pouch health

• A recent study examined an association of adherence to the Mediterranean Diet following colectomy and pouch formation & lower inflammatory markers
• Can diet promote pouch health through promotion of a healthy pouch microbiome?

Summary

• Consider symptoms and timing of onset of symptoms when choosing diagnostic tests to diagnose pouch disorders
• Successful treatment hinges on understanding underlying pouch dysfunction
• It may be time to start considering antibiotic-sparing strategies for chronic antibiotic dependent pouchitis
• Biologics have a role for chronic, antibiotic refractory pouchitis
• Perhaps – diet will emerge as an important disease modifying factor for our pouch patients
Questions?

Laura E. Raffals, MD, MS, FACG
Edward L. Barnes, MD, MPH

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