ACG Virtual Grand Rounds
Join us for upcoming Virtual Grand Rounds!

Week 19: Update on the Management of Upper GI Bleeding
John R. Saltzman, MD, FACG
July 30, 2020 at Noon EDT

Week 20: Management of Alcohol-Associated Liver Disease with Hepatology and Addiction Medicine
Ashwani K. Singal, MD, MS, FACG, and Jessica L. Mellinger, MD
August 6, 2020 at Noon EDT

Visit gi.org/ACGVGR to Register
Participating in the Webinar

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, 2020 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, 2021 for this activity.

ACG will submit MOC points on the first of each month. Please allow 3-5 business days for your MOC credit to appear on your ABIM account.

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.
Case #1

- 44-year-old man with metastatic pulmonary adenocarcinoma referred to clinic with now bloody diarrhea
- Started on pembrolizumab 6 months ago
  - Developed diarrhea 2 months later: 4-5 BM/day, loose, urgent
  - C. difficile PCR and Community Pathogens PCR negative
  - Treated with prednisone 100 mg daily with taper with resolution
  - Diarrhea returned when pembrolizumab restarted
    - C. difficile PCR and Community Pathogens PCR negative
  - Started on prednisone 100 mg (1 mg/kg) but diarrhea returned when tapered to 80 mg daily
  - 7-8 BM/day, loose, urgent and blood in > 50%
What is the next best step?

A. Start loperamide
B. Check CMV viral load
C. Increase prednisone to 2 mg/kg/day
D. Endoscopic evaluation
E. IV methylprednisolone

Colonoscopy

Pathology: Active colitis. Scattered epithelial apoptotic injury. No viral cytopathic effect is identified.

Note: All of the mucosa in this biopsy series shows some evidence of inflammatory and epithelial injury. In the biopsies of the right and left colon, there are scattered areas of neutrophilic cryptitis and crypt microabscess associated with epithelial apoptotic injury consistent with colitis secondary to PD-L1 inhibitor therapy

Diagnosis: Immune Checkpoint Inhibitor Mediated Colitis (ICI-C)

Case Continued

- Diarrhea persists after 3 days of IV methylprednisolone 2 mg/kg/day

Now what is the next best step?

A. Increase to methylprednisolone 3 mg/kg/day
B. Add ciprofloxacin and metronidazole
C. Start infliximab
D. Fecal microbiota transplant
E. Consult surgery for diverting loop ileostomy
Immune Checkpoint Inhibitors

- CTLA-4 and PD1/PDL1 are regulatory pathways that inhibit the immune response
  - Associated with tolerance and prevention of autoimmunity

- Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)
  - Ipilimumab, Tremelimumab

- Programmed cell death receptor-1 (PD-1)
  - Nivolumab, Pembrolizumab, Cemiplimab

- Programmed cell death ligand-1 (PD-L1)
  - Atezolizumab, Avelumab, Durvalumab

Images from www.cancer.gov

Immune Checkpoint Inhibitors

- Tumor cells may up-regulate suppressive signaling to T-cells via CTLA-4 and PD1 in order to evade the immune anti-tumor response
- Checkpoint inhibitors BLOCK these inhibitory signals thereby re-activating the immune response to tumor cells

Immune Related Adverse Events (irAEs)

- Activated T-cells can cross-react with host antigens → unique spectrum of adverse events (irAEs)
- Most common sites
  - Skin
  - Gastrointestinal
  - Colitis (ICI-C)
  - Hepatotoxicity
  - Endocrine
  - Pulmonary
ICl-C: Severity of Colitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Diarrhea Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase of &lt; 4 BM/day</td>
</tr>
<tr>
<td>2</td>
<td>Increase of 4-5 BM/day</td>
</tr>
<tr>
<td>3</td>
<td>Increase of ≥ 7 BM/day</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences</td>
</tr>
<tr>
<td></td>
<td>Hospitalization indicated</td>
</tr>
</tbody>
</table>

ICl-C: Timing and Incidence of Colitis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Grade 1 (%)</th>
<th>Grade 2/4 (%)</th>
<th>Grade 1 (%)</th>
<th>Grade 2/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of onset, weeks</td>
<td>6-8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-CTLA-4 monotherapy</td>
<td>23-33</td>
<td>3-6</td>
<td>8-12</td>
<td>7-9</td>
</tr>
<tr>
<td>Anti-PD-1/PD-L1 monotherapy</td>
<td>11-19</td>
<td>1-3</td>
<td>1-4</td>
<td>&lt;1-3</td>
</tr>
<tr>
<td>Combination Anti-CTLA-4 and Anti-PD-1/PD-L1</td>
<td>66-45</td>
<td>9-11</td>
<td>12-26</td>
<td>8-17</td>
</tr>
</tbody>
</table>

ICl-C: Clinical Features and Work up

- Colitis related mortality rate is 2-5%
- Watery diarrhea, urgency, incontinence, abdominal pain
- Laboratories: CBC, CMP, TSH, TTG IgA
- Stool studies: infectious work-up, fecal calprotectin
- CT scan abdomen/pelvis
  - Indications: Grade 3 or 4 diarrhea, severe abdominal pain, distension, peritoneal signs
  - Rationale: Rule out complications of colitis
- Findings: Bowel wall thickening, fat stranding, fluid filled colon, mucosal hyper-enhancement
ICI-C: Endoscopic Evaluation

- **Sigmoidoscopy/Colonoscopy**
  - Indications: Persistent Grade 2 diarrhea, Any Grade 3 or 4, Steroid refractory, Severe abdominal pain, Hematochezia
  - Findings: Endoscopic appearance is not specific: erythema, edema, mucosal friability, superficial ulcerations, erosions, can be segmental, can be normal
  - Histology: Not specific
    - Active colitis pattern: Neutrophilic inflammation, ↑ intraepithelial lymphocytes, ↑ apoptotic crypt epithelial cells (can resemble infectious colitis)
    - Lymphocytic colitis pattern: ↑ lamina propria lymphoplasmacytic inflammation, scattered crypt epithelial apoptosis (can resemble microscopic colitis)

ICI-C: Management Algorithm

Management Severe (Grade 3 / 4) ICI Colitis

- Discontinue checkpoint inhibitor
- IV fluids, electrolyte repletion
- Consider hospitalization
- High dose corticosteroids (1-2 mg/kg/day methylprednisolone)
- Evaluate for contraindications to anti-TNF therapy
- Convert to equivalent dose of prednisone
- Start IFX 5-10 mg/kg
- Alternative options: VDZ and MMF
- Perianal extension: IFX 5-10 mg/kg x 2 weeks
- No response: Colectomy for toxic megacolon or perforation
Virtual Grand Rounds

Back to Our Case

- Persistent symptoms despite discontinuation of pembrolizumab and high dose corticosteroids
- Started on infliximab 5 mg/kg

75 patients with irEC
- 52% received CS alone
- 48% received IFX + CS

Despite higher grade colitis in the IFX group (grade 3/4: 86% vs. 34%; p < 0.001), median times to diarrhea resolution were shorter.

Box plots of association between treatment for irEC and time to irEC symptom resolution

Median 3 vs. 9 days; p < 0.001

Case #2

- 70-year-old woman with hypothyroidism presents to the ED with acute onset abdominal pain followed by bloody diarrhea
- Medications: levothyroxine, conjugated estrogen
- She reports crampy abdominal pain with associated nausea and passage of 6-8 episodes of loose stool mixed with bright red blood clots
- Exam: Abdomen soft with mild tenderness in the left upper and left lower quadrants
- Laboratories: WBC 14.3, Hgb 11.8, CMP normal, Lactic acid 0.9
- Community Pathogens PCR and C. difficile PCR negative

Checkpoint Inhibitor Colitis: Take Home Points

- Gastrointestinal toxicities are common irAEs of checkpoint inhibitors
- Incidence much higher in anti-CTLA-4 than anti-PD-1/PD-L1 agents
- Early diagnosis and treatment is key to optimizing clinical outcomes
- Endoscopic evaluation indicated for: Persistent Grade 2 diarrhea, Any Grade 3 or 4, Steroid refractory, Severe abdominal pain, Hematochezia
- High dose corticosteroids are first-line therapy
- Infliximab is recommend for steroid dependent/refractory colitis
- Data for vedolizumab or mycophenolate for IFX refractory cases
What is the next best step in her management?

A. Repeat *C. difficile* testing
B. Ciprofloxacin and metronidazole
C. CT scan abdomen/pelvis with oral and IV contrast
D. Multiphasic CTA
E. Colonoscopy

Colon Ischemia (CI)
- Reduction in blood flow due to:
  - Acute arterial occlusion (embolic, thrombotic)
  - Venous thrombosis
  - Hypoperfusion of the mesenteric vasculature (non-occlusive)
- Type I
  - Majority of cases
  - Non-occlusive small-vessel disease
- Type II
  - Identifiable etiology - commonly associated with systemic hypotension, decreased cardiac output or cardiac/vascular surgery

Colon Ischemia: Risk Factors
- Surgery: aortic or abdominal surgery, prior resection for colon cancer
- CV: HTN, CHF, atherosclerosis, PVD, Atrial fibrillation
- Pulm: COPD
- GI: Diarrhea, constipation, IBS
- Endo: Obesity, DM
- Rheumatologic disease
- Hypercoagulable disorder
- Drugs: constipation inducing drugs (opioids), immunomodulators, illicit drugs (cocaine, amphetamines)
- Extreme exercise
Colon Ischemia: Clinical Features

- **Presentation:**
  - Sudden cramping, mild, abdominal pain
  - Urgent defecation, maroon/bloody < 24 hours
  - Left-sided disease: more blood, right-sided disease: more pain

- **Outcomes:**
  - Most cases are benign and self-limited
  - Isolated right-sided colon ischemia (IRCI) associated with higher mortality rates
  - Gangrenous colitis: 10% and fulminant colitis: 2.5%
  - Recurrence < 10%

Colon Ischemia: Laboratory Testing

- Decreased Hgb levels, low serum albumin and the presence of metabolic acidosis can be used to predict severity
- Recommended initial testing for suspected CI
  - Serum: Albumin, amylase, CBC, CMP, CK, lactate, LDH
  - Stool: C. difficile, Culture, O&P
- Routine testing for a coagulation disorder in most patients with CI isn’t necessary

Colon Ischemia: Imaging

- CT with intravenous and oral contrast should be ordered as the imaging modality of choice for patients with suspected CI
- Findings include bowel wall thickening, edema, and thumbprinting
- Pneumatosis and porto-mesenteric venous gas predict transmural infarction
- Vascular imaging studies not indicated in most CI patients
- CTA should be performed on any patient with suspected IRCI or in any patient in whom the possibility of AMI cannot be excluded
Colon Ischemia: Colonoscopy

- Early colonoscopy (48 h) with minimal air insufflation in suspected CI to confirm diagnosis
- Avoid in severe CI
- Use CT to evaluate distribution with limited colonoscopy to confirm diagnosis as necessary; procedure should be stopped at the distal-most extent of the disease
- Biopsies should be obtained unless gangrene
- Colonoscopy should not be performed in patients with peritoneal signs or evidence of gangrene or pneumatosis

Colon Ischemia: Colonoscopy for Prognostication

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Entire population (%)(n)</th>
<th>Pancolonic (%)(n)</th>
<th>Right colon (%)(n)</th>
<th>Transverse colon (%)(n)</th>
<th>Left colon (%)(n)</th>
<th>Distal colon (%)(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (days, median (range))</td>
<td>7 (1-15)</td>
<td>9(1-15)</td>
<td>6(1-15)</td>
<td>5(1-7)</td>
<td>6(1-15)</td>
<td>6(1-15)</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>19.8% (62)</td>
<td>30.4% (7)</td>
<td>44.3% (35)</td>
<td>18.8% (6)</td>
<td>5.9% (6)</td>
<td>10.4% (8)</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>11.8% (37)</td>
<td>21.7% (5)</td>
<td>20.3% (16)</td>
<td>12.5% (4)</td>
<td>6.9% (7)</td>
<td>6.5% (5)</td>
</tr>
</tbody>
</table>

**Disease Severity Criteria**

- **Mild**
  - Typical symptoms of CI with a segmental colitis not isolated to the right colon and with none of the commonly associated risk factors for poorer outcome if that are seen in moderate disease
  - Observation
  - Supportive care

- **Moderate**
  - Any patient with CI and up to 3 of the following factors:
    - Hypotension (systolic BP < 90 mmHg)
    - Tachycardia (heart rate > 100 beats/min)
    - Abnormal liver function test
    - Hgb < 12 g/dL
    - LDH > 350 U/L
    - Serum Na < 136 mEq/L
    - Mucosal ulceration on colonoscopy
    - Male gender
    - Broad-spectrum antibiotics
    - Consultation
    - Volume replacement
    - Observational cohort study

- **Severe**
  - Any patient with CI and more than the criteria for moderate disease or one of the following:
    - Perforation or portal venous gas on radiologic imaging
    - Gangrene on colonoscopy
    - Emergent surgical consultation
    - Transfer to ICU
    - Treatment failure
    - Broad-spectrum antibiotics
    - Emergent hospitalization

33 cases of biopsy proven ischemic colitis
Colon Ischemia: Take Home Points

- CI is common and usually benign
- IRCI is associated with worsened outcomes
- CT A/P with IV and oral contrast modality of choice for suspected CI
- Colonoscopy recommended to confirm diagnosis and prognostication
- Antibiotics for moderate to severe disease
- Emergent surgical consultation for severe disease

Case #3

- 64-year-old man with history of prostate cancer treated with external beam RT 3 years ago is referred for management of persistent rectal bleeding
- Colonoscopy confirms your suspicion for chronic radiation proctitis

Which of the following treatment options would you recommend?

A. Metronidazole
B. Butyrate enema
C. Sucralfate enema
D. Mesalamine enema
E. Oral mesalamine
Radiation Proctitis: Background

- Risk significantly greater with external beam RT > brachytherapy
- Doses < 45 Gy associated with few long term side effects
- Newer modalities for external beam XRT will hopefully minimize toxicity
- ~1-5% of patients treated with XRT for pelvic malignancy will develop chronic radiation proctitis (CRP)

Radiation Proctitis: Clinical Features

- Acute: during or within 6 weeks of radiation therapy
  - Direct mucosal damage
  - Diarrhea, mucous, urgency, tenesmus, bleeding uncommon
- Chronic: 9 months - 30 years after exposure
  - Progressive epithelial atrophy and fibrosis associated with chronic mucosal ischemia
  - Bleeding, mucous, tenesmus, urgency with incontinence, strictures
- Concomitant injury to the genitourinary tract or small bowel may lead to fistulas, SBO, or SIBO

Radiation Proctitis: Work-up

- Assess for recurrence of primary malignancy
- Endoscopic evaluation
  - Non-specific and mucosal biopsies are not diagnostic; help to exclude other causes
- Imaging: MRI if fistula suspected, CT if obstruction to exclude malignancy
CRP: Medical Treatment

- No large controlled trials for treatment options
- Topical therapy
  - Glucocorticoid enemas (e.g., hydrocortisone 100 mg twice daily) for tenesmus
  - Mixed data for SCFA enemas: some benefit with acute, not effective for chronic
- Sucralfate enema
  - RCT: Oral sulfasalazine + prednisolone enemas vs sucralfate enemas (2 gm twice daily)
    - Sucralfate enemas better tolerated and had a significantly better clinical response after 4 weeks
- Oral therapy
  - 5-ASA, metronidazole, pentoxifylline lacking data
- Hyperbaric oxygen: expensive and not widely available

CRP: Endoscopic Treatment

- APC effective in reducing short-term CRP symptoms
- Some data for bipolar electrocoagulation, radiofrequency ablation, Nd-YAG laser and cryotherapy
  - RCT: APC vs Bipolar: equal efficacy (92% vs 93%) but significantly more complications in the bipolar group (87% vs 33%)
- ASGE Guidelines endorse use of APC, bipolar electrocoagulation, heater probe and RFA

Radiation Proctitis: Take Home Points

- With newer modalities for radiation therapy, < 5% patients treated with radiation for pelvic malignancy will develop CRP
- Sucralfate enemas first line therapy for persistent bleeding in CRP
- Endoscopic therapy with APC for patients with bleeding despite enema therapy
Case #4

- 60-year-old woman is referred to your clinic with a 6 month history of diarrhea
- 4-7 BM/day loose, non-bloody. No associated abdominal pain or weight loss
- Responds somewhat to over the counter anti-diarrheal medications but she is taking loperamide 4 times daily and still has occasional accidents
- No significant medical history
- Medications: MVI, sertraline
- Laboratories: CBC and CMP unremarkable, normal TSH, negative TTG IgA

What is the next best step in her work-up?

A. Hydrogen breath testing
B. Upper endoscopy with duodenal biopsies
C. Flexible sigmoidoscopy with biopsies
D. Colonoscopy with biopsies
E. CT enterography

Microscopic Colitis: Clinical Features

- Two subtypes of Microscopic colitis (MC)
  - Collagenous colitis (CC) and Lymphocytic colitis (LC)
  - Unclear if distinct or parts of a spectrum
- Most common symptom is intermittent watery diarrhea
- Almost half will have concomitant abdominal pain, wt loss or arthralgias
- Average age at diagnosis 50-70 yrs, female predominance
- Association with NSAIDs and other medications
- Association with celiac disease and other autoimmune conditions
Predictors of Microscopic Colitis

- Factors that increase the probability of MC
- Age > 50
- Nocturnal bowel movements
- Weight loss
- Diarrhea < 12 months
- Introduction of a new drug
- Known autoimmune disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of autoimmune disease</td>
<td>4.0 (2.1-7.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Introduction of new drug within 3 months of diarrhoea onset</td>
<td>3.7 (2.1-6.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age &gt; 50 years</td>
<td>3.4 (1.9-6.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2.2 (1.2-3.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diarrhea &lt; 12 months</td>
<td>2.9 (1.3-5.8)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Microscopic Colitis and Celiac Disease

- Up to 1/3 patients with Celiac Disease have MC-like histologic changes on colon biopsies
- Consider MC in patients with Celiac Disease not responding to a strict GFD
- Only 2-9% patients with MC have Celiac Disease
- Not necessary to screen every MC patient
- When suspected (steatorrhea, iron deficiency anemia, non-responder): obtain SB biopsies instead of celiac serologies

Microscopic Colitis: Drug Induced

- High likelihood
  - PPIs, NSAIDs, H2RAs, SSRIs
- Intermediate likelihood
  - Carbamazepine, Flutamide, Lisinopril, Statins
**Microscopic Colitis: Diagnosis**

- Diagnosis made by histology
  - LC: > 20 intraepithelial lymphocytes/100 surface cells, mixed acute/chronic infiltrate
  - CC: intraepithelial lymphocytes less prominent, thickened subepithelial collagen band > 7 μm (nl ≤ 5 μm)
- Recommend at least 8 biopsies from different segments of colon

**Microscopic Colitis: Treatment**

- Budesonide is the best-studied treatment for MC (6 RCTs)
  - Response 80% vs 20% placebo
  - Relapse common (60-80%)
  - Maintenance may be required
    - 3 RCTs showed budesonide (4.5-6 mg/day) was superior to placebo for maintenance through 6-12 months
    - Taper to lowest effective dose

**Budesonide Non-Responders**

- Incorrect diagnosis
- Review slides with GI pathologist
- Drug-induced microscopic colitis
- Non-compliance
- Evaluate for other causes diarrhea
- Treatment options
  - Trial prednisone or a bile acid binder
  - Immunosuppressive agents
  - Recent data disappointing
Microscopic Colitis: Take Home Points

- MC is a common cause of watery diarrhea; especially in older women
- Remember association with Celiac Disease
- Remember medications associated with MC (PPIs and SSRIs)
- Diagnosis with biopsies from the right and left colon
- Induction therapy with bismuth or budesonide
- Budesonide maintenance therapy is often required

Thank you!

Questions?

Moderator: 
Anita Afzali, MD, MPH, FACG

Speaker: 
Anne G. Tuskey, MD, FACG
ACG Telehealth Survey
Your Input Needed

Telehealth Usage in GI: Before, During and After COVID-19

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