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, 2023 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, 2024 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.

ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 9 – Thursday, March 2, 2023
Best of ACG 2022! Outstanding Science, Expert Discussions
Moderators: Vivek Kaul, MD, FACG and Vladimir M. Kushnir MD
Faculty: Amer AlSamman, MD; Adam Buckholz, MD; Daniel Castaneda, MD; Sarah M. Enslin, PA-C; and Daniela Guerrero Vinsard, MD
Panelists: Prabhleen Chahal, MD, FACG; Jean Chalhoub, MD; Ryan B. Perumpail, MD; Aparna Repaka, MD; Brandon A. Wuerth, MD
At Noon and 8pm Eastern
Visit gi.org/ACGVGR to Register
Disclosures

Max J. Schmulson, MD
- Alfasigma Mexico: Advisory Board, Grant Support, Speakers Bureau;
- Carnot: Speakers Bureau;
- Ferrer Central America: Grant Support, Speakers Bureau;
- Gemelli Biotech: Advisory Board, Consultant;
- Laboratorios Tecnofarma SA Bolivia: Speakers Bureau;
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*All of the relevant financial relationships listed for these individuals have been mitigated*
Post-COVID-19
Disorders of Gut-Brain Interaction (DGBI)/Functional Gastrointestinal Disorders (FGID)

Dr. Max Schmulson W.
Professor of Medicine
Laboratory of Liver, Pancreas and Motility (HIPAM)-Unit of Research in Experimental Medicine, Faculty of Medicine-Universidad Nacional Autónoma de México (UNAM). Gastroenterology and Endoscopy, American British Cowdray (ABC) Medical Center. Gastroenterology and Gastrointestinal Motility, Clínica Lomas Altas. Mexico City

maxjulio@prodigy.net.mx, mschmulson@Gmail.com

Síntomas GI en COVID-19

Nausea
Vomiting
Burping
Heartburn
Abdominal pain
Anorexia
Bloating/Distension
Diarrhea

Figure by Marco Gudiño-Zayas and Max Schmulson
Unit of Experimental Medicine, Faculty of Medicine-UNAM. 2020.
Hemorrhagic Colitis because of SARS-CoV-2

a. Small pleural effusion. b, c, d. Severe transmural inflammation of the ascending, transverse and descending colon

SARS-CoV-2 faringal swab and stools of 42 patients

ACE2 expression pattern in bulk tissues and cell lines

Higher expresión of the ACE2 receptor in absorption related-enterocytes and in the pits of the terminal ileum of 13 children with DGBI
SARS-CoV-2, ACE2 and serin proteases receptors

740 amino acid soluble (sACE2) circulating form (decoy receptor for MERS-CoV-2)

805 amino acid membrane-spanning molecule

The membrane-anchored protease important for activation of the SARS-CoV-2 S protein

Histological and immunofluorescent staining of the ACE2 receptor and the viral nucleocapsid protein (NP) of SARS-CoV-2 in the GI tract

Viral host receptor ACE2 is rarely expressed in esophageal epithelium but abundantly in cilia of glandular epithelia

Similar findings were observed for the viral nucleocapsid protein in the cytoplasm of GI epithelium
Infection of SARS-CoV-2 in ACE2+ mature enterocytes in human small intestinal and colonic organoids

Using a chimeric vesicular stomatitis virus (VSV) in which the native glycoprotein (G) was genetically replaced with SARS-CoV-2 S protein

Enteroids were stained for:
- Virus (green)
- Actin (phalloidin, white)
- Nucleus (DAPI: 4',6-Diamidino-2-phenylindole, blue)

Fecal calprotectin indicates intestinal inflammation in patients with COVID-19

Changes in intestinal microbiota of patients with COVID-19 without antibiotic treatment

*Downregulate the expression of ACE2 in the murine gut, and correlated inversely with the viral load in fecal samples of hospitalized patients
Alterations in fecal fungal microbiome in patients with COVID-19

Proposed mechanism for Post-COVID-19 FGIDs/DGBI

Proposed diagnostic criteria for Post-COVID-19 FGIDs/DGBI

1. Fulfilling Rome IV criteria for any FGID in the last 3 months, with symptom onset at least 6 months before diagnosis associated with:
   a. Previous COVID-19 infection confirmed by SARS-COV-2 Real Time-PCR performed at Regional Reference Laboratories
   b. Symptom development immediately after resolution of acute COVID-19 infection

2. Should not meet criteria for FGIDs before onset of acute illness

FGIDs: Functional gastrointestinal disorders; DGBI: Disorders of Gut-Brain Interaction; COVID-19: Coronavirus Disease 2019, SARS-CoV-2, Severe acute respiratory syndrome - Coronavirus - 2; PCR, Polymerase chain reaction
### Effects of home confinement and social distancing in the general population: Syst. Rev. 26 studies

**Anxiety**
- Prevalence: 8.3% to 45.1%

**Depression**
- Prevalence: 14.6% to 46.4%

**Most vulnerable ones:**
- Females, Younger age, Unemployed, Previous mental health or psychiatric illnesses

---

### Mental disorders following COVID 19 and other epidemics: Syst. Rev and Metaanalysis 247 on COVID 19

**Probable Anxiety**
- Prevalence: 20.7% (IC 95% 12.9-29.7)

**Probable Depression**
- Prevalence: 18.1% (IC 95% 13.0–23.9)

**Psychological Dystress**
- Prevalence: 13.0% (IC 95% 0–34.1)

**Most vulnerable ones:**
- Female sex, Lower income, Pre-existing medical conditions, Perceived risk of infection, Exhibiting COVID-19-like symptoms, Use of social media, Financial stress, Loneliness

---

### The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis

31 Studies (5153 patients)

- Depression: 45% (95% CI: 37–54%, $I^2 = 96\%$)
- Anxiety: 47% (95% CI: 37–57%, $I^2 = 97\%$)
- Sleep disturbances: 34% (95% CI: 19-50%, $I^2 = 98\%$)

Lack of contact with families and loved ones during quarantine or hospitalization
Fear relating to the disease due to poor knowledge or misinformation regarding to COVID-19
Feeling of self-blame and social stigma

Gut microbiota composition reflects disease severity and dysfunctional immune responses patients with COVID-19

Decrease representation of immunomodulator commensals: Faecalibacterium prausnitzii, Eubacterium Rectale, y Bifidobacterias

CXCL10: C-X-C Motif Chemokine Ligand 10 or Interferon gamma-induced protein 10
NT-pro BNP: N-terminal prohormone of Brain Natriuretic Peptide


Gut Dysbiosis

Postacute COVID-19 is Characterized by Gut Viral Antigen Persistence in Inflammatory Bowel Diseases

46 IBD patients with PCR-confirmed SARS-CoV-2 were scoped (upper and lower) 94–257 days (average, 7.3 months) after infection.


• 2100 Studies were identified / 57 were selected including 250351 survivors of COVID-19 (79% hospitalized)
• 45 Studies were from countries with high socioeconomical level
• Age: 54.4±8.9 years, Men: 140196 (56%)


Digestive Disorder

- Abdominal pain
- Diarrhea and constipation
- Decreased appetite

Chest abnormalities-Imaging, median [IQR]: 62.2% [45.8-76.5%]
Functional Impairment: 44.0% [23.4-62.6%]
Fatigue/Muscular Weakness: 37.5% [25.4-54.5%]
Concentration problems: 23.8% [20.4-25.9%]
Anxiety disorders: 29.6% [14.0-44.0%]
Gastrointestinal sequelae 90 days after discharge for COVID-19 in patients in China

- Study in 12 hospitals from Hubei and Guandong (between 16-01 and 7-03, 2020)
- 117 patients
- 45% older than 60
- 52 (44%) reported GI sequelae at discharged (only 1 reported resolution at 90 days)


GI symptoms one month post-COVID-19

871 of 2036 hospitalized patients in Europe:
575 COVID-19 +
296 COVID-19 -

Frequency and Severity of digestive Symptoms in COVID 19 + and -

Related factors:
- Female sex
- Higher BMI
- Dyspnea
- High CRP

GI, Extra-GI, and Psychological manifestations after the resolution of SARS-CoV-2 in patients with COVID-19 With vs. Without Diarrhea

**IGI:**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>IGI Positive</th>
<th>IGI Negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain/discomfort</td>
<td>0.46 ± 0.69</td>
<td>0.29 ± 0.36</td>
<td>0.016</td>
</tr>
<tr>
<td>Diarrhea/constipation</td>
<td>0.39 ± 0.63</td>
<td>0.20 ± 0.26</td>
<td>0.000</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease/</td>
<td>0.26 ± 0.55</td>
<td>0.22 ± 0.40</td>
<td>0.009</td>
</tr>
<tr>
<td>Dyspeptic symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-specified</td>
<td>0.17 ± 0.36</td>
<td>0.14 ± 0.29</td>
<td>0.56</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.32 ± 0.59</td>
<td>0.31 ± 0.42</td>
<td>0.59</td>
</tr>
</tbody>
</table>

**IGI-extra-GI:**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>IGI Positive</th>
<th>IGI Negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite</td>
<td>2.7 (2.0%)</td>
<td>9.3 (7.7%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Headache</td>
<td>34 (6.9%)</td>
<td>10 (13.7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>38 (6.7%)</td>
<td>22 (3.1%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td>32 (6.7%)</td>
<td>17 (2.5%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Depression</td>
<td>7.0 (2.1%)</td>
<td>3.6 (1.9%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>15.7 (4.0%)</td>
<td>15 (3.3%)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**IGI-X:**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>IGI Positive</th>
<th>IGI Negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood</td>
<td>4.3 (1.6%)</td>
<td>3.3 (1.9%)</td>
<td>0.097</td>
</tr>
</tbody>
</table>

**IGI-X2:**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>IGI Positive</th>
<th>IGI Negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood</td>
<td>4.3 (1.6%)</td>
<td>3.3 (1.9%)</td>
<td>0.097</td>
</tr>
</tbody>
</table>

**IBS by Rome IV:** 26.2% in patients With vs. Without Diarrhea during COVID-19

**Digestive symptoms and DGBI Post-COVID-19**

**Digestive Symptoms Post COVID-19 (%)**

- **One month Post COVID-19:**
  - Bowel symptoms: 8.6%
  - Dyspeptic symptoms: 5.7%
  - Overlap: 3.9%

- **Three months Post COVID-19:**
  - Bowel symptoms: 5.7%
  - Dyspeptic symptoms: 3.9%
  - Overlap: 2.1%

**DGBI 6 months Post COVID-19 (%)**

- **Post COVID-19 (n=280):**
  - IBS: 5.3%
  - Non Investigated Dyspepsia: 2.1%
  - Overlap: 1.8%

- **Hysterotic controls (n=264):**
  - IBS: 0.4%

**Risk factors:**
- Anosmia, Ageusia, Bowel symptoms, Dyspeptic symptoms, or Overlap at 3 months, and Psychological comorbidities.

Noviello D y cols. Neurogastroenterol Motil. 2022;34:e14187.
Development of DGBI in patients with Asymptomatic vs. Symptomatic COVID-19, and in those With vs. Without GI Symptoms

Figure 3: Kaplan-Meier curves showing the development of functional gastrointestinal disorders (e.g., irritable bowel syndrome (IBS), uninvestigated dyspepsia (UD), and their overlap) at 6 month follow-up (a) among asymptomatic compared to the asymptomatic patients with coronavirus disease-19 (COVID-19), and (b) among those with and without gastrointestinal (GI) symptoms. (a) Asymptomatic, Symptomatic. (b) No GI symptoms.

Post COVID-19 DGBI and associated factors in a hospital from a USA metropolitan area (Suffolk county)

- Retrospective study 6 months post COVID-19 that occurred between April and September 2020
- Patients were contacted by phone (those with previous dyspeptic or IBS symptoms, or with organicity that could explain the symptoms)
- English or Spanish speaking patients
- Determine the presence of Dyspepsia-like or IBS-like, by Rome-IV
- 891 patients identified
  - Met inclusion criteria (n): 459
  - Fulfilled screening (n): 272 (72 were excluded because of previous symptoms)
  - Analyzed (n): 200

Post COVID-19 DGBI and associated factors in a hospital from a USA metropolitan area (Suffolk county)

Internet study of 2 Phases

- **Phase 1**: Patients with COVID-19 (n=1114)
  - Demographics, comorbidities, symptoms, complications, hospitalization

- **Phase 2**: Determine the presence of Post COVID-19 DGBI by Rome IV (n=164), Association with Anxiety (GAD-7) and Depression (PHQ-9)
  - Uni and Multivariate analyses identified 5 Groups of patients based on: GI Symptoms, Anosmia and Chest Pain
  - The presence of GI symptoms were independent predictors of COVID-19, but not always correlated with known factors of severity such as Age>65, Diabetes Mellitus, Deficiency of Vit D
Depression (65%), but not Anxiety (48%), was more common in those with DGBI Post-COVID-19.

Functional Dyspepsia

Subtypes (n)

- 16
  - Postprandial Distress S.
  - Epigastric Pain S.
  - Mixed

- 14
  - IBS-D
  - IBS-C
  - IBS-M
  - IBS-U

Risk factors for IBS 12 months Post COVID-19

<table>
<thead>
<tr>
<th>Factor</th>
<th>RM (95%) IC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alergias</td>
<td>10.024 (1.766, 56.891)</td>
<td>0.009</td>
</tr>
<tr>
<td>PPIs</td>
<td>4.816 (1.447, 16.025)</td>
<td>0.010</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4.157 (1.336, 12.934)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Other factors that were studied: Chronic liver diseases, Antibiotics, Cough, Anxiety by the HAD 6 months before

Marasco G et al. Gut 2022; In press.
Anxiety and depression by the HAD scale after 6 and 12 months in patients hospitalized with COVID-19 and controls

Marasco G et al. Gut 2022; In press.

Diarrhea because of C. difficile: A differential diagnosis from diarrhea Post COVID-19

The Impact of COVID-19 Pandemic on Neurogastroenterologists in Latin America
Results of an Online Survey

Max Schmulson, MD, RFF*, Marco Gualiño-Zayas, DST†, Abis Han, MD,‡
and The Sociedad Latinoamericana de Neurogastroenterologia (SLNG)

- All reported a negative impact in their practice, **88.6% a reduction of 61%-100% mainly** in consultations and endoscopies
- Reasons for a negative impact in their GI practice: Patients fear, mandatory lockdown, physicians own decision, to prevent infection spreading
- Decrease in emergency endoscopies in 33.3%, in Manometries/pH only 4%
- Telemedicine: Implemented by 83%, but only 64.7% were reimbursed
- Mobilization of Gastroenterologists to COVID-19 wards: 11.5%
- Anxiety and Depression because of the pandemic: 78.7%
- Increase in consultations for FGIDs/DGBI: **36.1%**
- Differences by countries: Colombia, mandatory lockdown (p=0.001); México, higher frequency of treating patients with COVID-19 (p=0.053); México/Colombia, mobilization to COVID-19 wards (p= 0.012); Brazil, lower prohibition for elective procedures (p=0.012) and reimbursement for Telemedicine (p=0.034)

Increase in gastrointestinal symptoms and use of healthcare resources in patients with DGBI and gastroparesis during the COVID-19 pandemic

Increased prevalence of GI symptoms and DGBI during the COVID-19 pandemic: An internet-based survey in Bulgaria

Survey 1, 2019 - Normal circumstances
Survey 2, 2020 - COVID-19 lockdown

GI Symptoms:
- Lower risk in >80 vs. 18-79 years: OR 0.41, p<0.01
- Higher risk in patients With IBS vs. Without IBS: OR 7.7, p=0.02
- Higher risk in Midwest vs. Other regions of the USA: OR 1.66, p=0.06

Diarrhea:
- Lower risk in >80 vs. 18-79 years: OR 0.43, p<0.01
- Higher risk in IBS vs. Without IBS: OR 6.72, p<0.01
- Higher risk With vs. Without Constitutional Symptoms: OR 2.15, p=0.001
- Higher risk With vs. Without Immunosuppressors: OR 1.56, p=0.02
- Lower risk With vs. Without Diabetes: OR 0.69, p=0.01

IBS as a risk factor for GI symptoms and diarrhea in patients with COVID-19 in the USA

Registry of 1992 patients hospitalized for COVID-19, 1406 were eligible

Factors associated with GI symptoms (%)

- Non Hispanics/Latinos
- Hispanics/Latinos
- <70 years
- >70 years
- Constitutional symp
- Without Constitutional Sympt
- IBS
- Without IBS

Multivariate analysis

GI Symptoms:
- Lower risk in >80 vs. 18-79 years: OR 0.41, p<0.01
- Higher risk in patients With IBS vs. Without IBS: OR 7.7, p=0.02
- Higher risk in Midwest vs. Other regions of the USA: OR 1.66, p=0.06

Diarrhea:
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- Higher risk With vs. Without Immunosuppressors: OR 1.56, p=0.02
- Lower risk With vs. Without Diabetes: OR 0.69, p=0.01
Impact of COVID-19 on gastrointestinal symptoms in patients with Functional Dyspepsia and IBS vs. Controls

Internet survey in 5157 subjects in Japan in May 2020, 8.5% with Functional Dyspepsia (FD), 16.6% with Irritable Bowel Syndrome (IBS) and 4% with FD-IBS overlap

- During the pandemic, 11.9% reported deterioration of GI symptoms and 2.8% improvement

- Factors associated with deterioration: FD-IBS overlap (the most important one), psychological comorbidities, stress at work/school

- Factors associated with improvement: Younger age, commuting by public transportation as usual, work/study from home

Impact of the COVID-19 pandemic and lockdown stress on psychological aspects and quality of life in subjects With vs. Without IBS in France

Survey among members (n=794) of the French Association of Patients that Suffer of IBS (Association des patients souffrant du syndrome de l'intestin irritable [APSSII]), and family and friends

<table>
<thead>
<tr>
<th>Consequences</th>
<th>IBS (n=232)</th>
<th>Without IBS (n=72)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (HAD)</td>
<td>10.6±3.9</td>
<td>6.9±3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression (HAD)</td>
<td>7.3±3.85</td>
<td>4.8±3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAD Global</td>
<td>17.8±6.5</td>
<td>11.8±6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue (0-7)</td>
<td>4.9±1.5</td>
<td>3.6±1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep disturbances (%)</td>
<td>61.5</td>
<td>53</td>
<td>0.216</td>
</tr>
<tr>
<td>New sleep disturbances</td>
<td>12</td>
<td>9.1</td>
<td>0.216</td>
</tr>
<tr>
<td>Increase in the sleep disturbances</td>
<td>27.7</td>
<td>13.6</td>
<td>0.038</td>
</tr>
<tr>
<td>IBS-QOL (0-100)</td>
<td>47.6±19.9</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>QOL in general</td>
<td>77.8±16.8</td>
<td>52.2±27.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Conclusiones

• GI symptoms are very frequent in COVID-19. The main reason for that is the presence of the ACE2 receptor that is required for the attachment of the SARS-CoV-2 spike (S) glycoprotein to the human cells and further released their viral components, and their highest expression within the human body is in the intestinal epithelial cells.

• The inflammation in the gut, increased permeability, dysbiosis, and psychological stress triggered by COVID-19, and the remaining of unviable viral particles, are all potential mechanisms for the development of Post-COVID-19-DGBI.

• The GI sequels of COVID-19 and the development of Post COVID-19 DGBI, have already been reported globally. The variability in their prevalence is due to the differences in the design and methodology of the studies. Therefore, physicians and gastroenterologists need to be aware of these possibilities.

• C. difficile infection needs to be ruled out in patients with newly developed Post COVID-19, especially if they were hospitalized or received antibiotics.

• Also, the history of DGBI predisposes to a higher frequency of GI symptoms during COVID-19, higher psychological distress, lower quality of life, and as a consequence, a higher use of healthcare resources by these patients.
CONNECT AND COLLABORATE IN GI

ACG & CCF IBD Circle
ACG Hepatology Circle

ACG GI Circle
Connect and collaborate within GI

ACG Functional GI Health and Nutrition Circle
ACG Women in GI Circle

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53