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Eosinophilic Gastrointestinal Diseases: Beyond EoE
Nirmala Gonsalves, MD, AGAF, FACG

While great strides have been made in the last few decades to improve our understanding of the diagnosis and treatment of eosinophilic esophagitis (EoE), there is much to be learned about treating other non-EoE eosinophilic gastrointestinal diseases (EGIDs). One of the first challenges in diagnosing these rare conditions was developing a consistent nomenclature. For instance, previously, the term “eosinophilic gastroenteritis” was used broadly to encompass diverse instances of eosinophilic infiltration within the gastrointestinal tract. However, this broad application and lack of standardized criteria resulted in diagnostic ambiguity and confusion. To help improve clinical and research advances in disorders of eosinophils below the diaphragm, in 2022 an international committee convened to create a consensus on standardizing EGID nomenclature. This important milestone created an EGID nomenclature system to specify the location of inflammation in a more precise and defined way. Additional challenges with diagnosing and managing non-EoE EGIDs include the heterogenous symptom presentation, which can lead to delay in diagnosis. Furthermore, the lack of an FDA-approved treatment for non-EoE EGIDs creates additional hurdles for treatment.

Standardizing EGID Nomenclature

The first step in developing these guidelines was convening a multidisciplinary committee that included 91 experts from 5 continents, spanning the fields of adult/pediatric gastroenterology, allergy, and pathology, as well as other key stakeholders. The first observation was that within the committee alone, there were 15+ interpretations for the term “eosinophilic gastroenteritis.” If the term “eosinophilic gastroenteritis” is used, it should only refer to “stomach and small bowel involvement.” However, the preferred terminology would involve a more specific breakdown of organ location.
EGID Location and Condition

**Esophagus →**
Eosinophilic Esophagitis (EoE)

**Stomach →**
Eosinophilic Gastritis (EoG)

**Small bowel →**
Eosinophilic Enteritis (EoN)

**Colon →**
Eosinophilic Colitis (EoC)

Multiple Areas of Involvement

Naming consensus not reached for overlapping stomach and esophageal involvement.

Eosinophilic Gastritis and Enteritis
Eosinophilic Gastritis and Duodenitis

Eosinophilic Duodenitis (EoD)
Eosinophilic Jejunitis (EoJ)
Eosinophilic Ileitis (EoI)

Eosinophilic Gastritis and Colitis
Eosinophilic Duodenitis and Colitis
Eosinophilic Ileitis (EoI)

Multiple naming convention applies when both possible locations are affected.

EoE vs non-EoE EGIDs

<table>
<thead>
<tr>
<th>EoE</th>
<th>Both</th>
<th>Non-EoE EGIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two FDA-approved treatments available</td>
<td>Similar pathophysiology</td>
<td>No FDA-approved treatments</td>
</tr>
<tr>
<td>Male predominance</td>
<td>Affect patients at any age</td>
<td>Heterogeneous symptoms</td>
</tr>
</tbody>
</table>

Clinical Presentation of Non-EoE EGIDs

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal</td>
<td>Muscularis</td>
</tr>
<tr>
<td>EoG</td>
<td>• Early satiety&lt;BR&gt;• Epigastric pain&lt;BR&gt;• Dyspepsia&lt;BR&gt;• Failure to gain weight&lt;BR&gt;• Oral aversion&lt;BR&gt;• Vomiting</td>
</tr>
<tr>
<td>EoN</td>
<td>• Abdominal pain&lt;BR&gt;• Bloating&lt;BR&gt;• Diarrhea&lt;BR&gt;• Dyspepsia&lt;BR&gt;• Hematemesis&lt;BR&gt;• Vomiting</td>
</tr>
<tr>
<td>EoC</td>
<td>• Abdominal pain&lt;BR&gt;• Diarrhea or constipation&lt;BR&gt;• Lower GI bleeding&lt;BR&gt;• Tenesmus</td>
</tr>
</tbody>
</table>
Non-EoE EGID Treatment Outcomes

Clinical Improvement With Dietary Therapy
A prospective study of an elemental diet in adult patients with EoG and EoN showed histologic remission and improvement in endoscopic change, symptoms, molecular parameters, and quality of life.
In one small study, patient compliance with elemental diet reached 100%, with perceived effort decreasing from 81% to 37% by week 5.

Proton Pump Inhibitor (PPI) Therapy
Thought to suppress acid-related aggravation of gastroduodenal lesions.
In a retrospective series of adult and pediatric patients with non-EoE EGIDs, > 60% were initially treated with a PPI.
Efficacy and response mechanisms need to be further tested and confirmed.

Systemic Glucocorticoid
Doses of 20-40 mg daily are effective at achieving remission.
However, relapse is common with dose reduction.
Development of topical corticosteroids with crushed budesonide has been investigated, similar to the use of oral viscous budesonide in EoE.

Other Medical Therapies
Biological therapies for non-EoE have shown promise to be effective for improving eosinophil count based on preliminary studies.
Immunomodulators, leukotriene inhibitors, and mast cell stabilizers have been used with variable results.

Additional Considerations in Non-EoE EGID

Natural History Studies Suggest...
- EGIDs are chronic in nature.
- Most patients have a long duration of disease prior to presentation.
- The patchy nature of the disease contributes to delay in diagnosis.
- Multiple biopsies in the stomach and duodenum are required to accurately diagnose non-EoE EGIDs.

Endoscopic Features of Non-EoE
- EGIDs that prompt biopsies
- Gastric erythema
- Erosions/ulcerations
- Nodularity
- Friability
- Granularity
- Thickened folds
The Changing Face of IBD: Beyond the Western World

Gilaad G. Kaplan, MD, MPH, Paulo Kotze, MD, MS, PhD, and Siew C. Ng, MBBS, PhD

Inflammatory bowel disease (IBD) has become a global disease, with rising incidence in non-Western cohorts such as Asia and Latin America. These newly industrialized countries are in an “acceleration in incidence” stage, while Western countries are in a “compounding prevalence” stage as new cases level out, but prevalence climbs steadily. Incidence is varied throughout Asia and remains comparatively lower than in Western countries; this discrepancy is influenced by environmental risk factors such as diets high in fat, animal protein, sugar, fast food, and food additives, which are common in the Western world. In Latin America and the Caribbean, the incidence of IBD is also increasing, but is still less than in Western countries, and variance between countries depends on the level of urbanization and industrialization. Risk factors are like those of Asia, and also include inadequate living conditions, the absence of exposure to infectious diseases, treated water, and a limited ability to differentiate the diagnosis of infectious diseases, representing a key difference compared with the Western world. Treatment within these groups seems to be similarly effective compared with the Western world, although some areas of Asia and Latin America face more barriers to accessing healthcare, which is a key area that global health care could target.

Global Trends in IBD

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence per 100,000</th>
<th>Western World: Compounding prevalence</th>
<th>Developing Countries: Emergence stage</th>
<th>Newly Industrialized Countries: Incidence acceleration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>97.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>100.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>843.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>449.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>816.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>18.6 (UC)</td>
<td></td>
<td>57.3 (UC)</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>44.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>38.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>721.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>653.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Numbers represent prevalence of all IBD cases combined, unless otherwise noted as CD (Crohn’s disease) or UC (ulcerative colitis).

**Globally Understood Risk Factors**
- Smoking history
- Ultra-processed foods
- Living in an urban environment

**Extraintestinal Manifestations**
- Ankylosing spondylitis
- Fatigue
- Arthritis
- Uveitis
- Sacroiliitis
- Primary sclerosing cholangitis (lower rates in Asia)
- Pyoderma gangrenosum
- Erythema nodosum
IBD in the Western World\textsuperscript{2,5-7,17-19}

**Most Studied Risk Factors**
- Less active lifestyle
- Oral contraceptive use
- Ultra-processed food
- Antibiotic use during childhood

**Presentation of Disease**
- IBD is diagnosed at all ages, but predominantly in young individuals.
- **Inflammatory Crohn's disease** is most common, but complications like perianal fistulizing disease and extra-intestinal manifestations may present at diagnosis.

**Genes Involved**
- NOD2
- IL-23R
- ATG16L

Data indicate a weaker heritable component for ulcerative colitis, while NOD2 is stronger for Crohn's disease.

**Differential Diagnosis**
- Intestinal tuberculosis
- Yersiniosis
- Actinomycosis
- Sexually transmitted infections (STIs)
- Histoplasmosis
- Amoebiasis
- Helminthiasis
- Ischemic colitis
- Vasculitis

IBD in Asia\textsuperscript{2,6,7,20-27}

**More Commonly Diagnosed in . . .**
- Younger patients
- Female patients

**Most Studied Risk Factors**
- Fat, cholesterol, and fatty acids
- Eggs, meats, fish, and meat products

**Genes Involved**
- TNSF-F15
- NOD2 and ATG16L1 are less common

**Presentation of Disease**
- The ratio of ulcerative colitis to Crohn's disease cases is \textit{approaching 1:1}.
- About \textbf{1 in 3 patients} with Crohn's disease have complicated disease behavior/perianal manifestations at diagnosis.
- High rates of ileocolonic disease are observed.

**Differential Diagnosis**
- Intestinal tuberculosis
- Infectious diseases (bacterial, protozoal, helminth infestations)
- Yersiniosis
- Actinomycosis
- Histoplasmosis
- Strongyloidiase
- Amebiasis
- STIs
- Hepatitis B
More Commonly Diagnosed in . . .

- Female patients

Genes Involved

Not enough data exist at this time on the genetic basis and interaction with environment in this population, although a gene-environment interaction is suspected as a cause of disease.

Presentation of Disease

- The most common Crohn’s disease phenotypes are inflammation, stricturing, penetrating, and perianal disease.
- Extraintestinal manifestations occur in nearly 40% of patients.

Differential Diagnosis

- Parasitic infectious diseases (protozoa and helminths)
- Intestinal amebiasis (*Entamoeba histolytica*)
- Strongyloidiasis
- Tuberculosis

Global Access to Treatment and Resources

Despite the wide array of possible treatments for IBD—including mesalamine, immune system suppressors, biologics, oral small molecules, nutritional supplements, and surgery—access to care varies greatly around the world.

While these treatments are generally widely available for patients in the Western world, Asian and Latin American populations have less extensive health care infrastructures, making it much more difficult to receive proper diagnosis and therapy.

Global disparities are also due to pharmaceutical pricing, access to biosimilars, and national drug policies and approvals. Investment in new drugs and technology is expensive and limits the distribution of drugs in some countries.
The Role of Noninvasive Biomarkers: Evaluation and Management of MASLD

Julia J. Wattacheril, MD, MPH

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), refers to a range of liver conditions characterized by the accumulation of fat in the liver due to metabolic factors. MASLD affects nearly 30% of the global population and is a prevalent cause of advanced liver disease. This disease can progress from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), which involves inflammation and liver cell damage—and unmitigated can lead to liver cirrhosis, liver failure, and liver cancer.

Clinicians’ early identification and stratification of at-risk individuals may impact progression and regression, as only a minority of individuals with MASLD present with liver-related consequences. Although early identification and risk stratification may occur in gastroenterology and hepatology clinics, disease modifying interventions may occur outside of those settings. Continuously monitoring MASLD response to current treatments is also key. Histologic examination of the liver is the current established standard for assessing and monitoring this disease, grading necroinflammation, and staging hepatic fibrosis; however, the cost and invasiveness limit its routine and widespread use. Drug approvals independent of histology-based outcomes lay the groundwork for further standardization and validation of noninvasive tests (NITs) in the evaluation and management of MASLD.

The latest AGA Clinical Practice Update (2023) can help healthcare professionals use NITs to identify patients who are at higher risk for MASLD progression for directed intervention. Ongoing research continues to refine the use of NITs in evaluating and managing MASLD; therefore, the landscape is likely to evolve and advance over time.

Utilization of Noninvasive Biomarker Testing

- Confirm Diagnosis: Identify at-risk patients
- Exclude Alternative Causes
- Risk Stratification: Tailors interventions and follow-up plans based on patient’s risk profile
- Monitoring Disease Progression/Regression: Helps identify high-risk and advanced fibrosis
- Response to Treatment: Assesses the effectiveness of therapies and interventions
Noninvasive Biomarkers for MASLD Evaluation and Risk Stratification

Serum-Based Biomarkers

- Fibrosis 4 Index (FIB-4) score
- NAFLD fibrosis score
- Aspartate aminotransferase to platelet ratio index (APRI)

Proprietary

- FIBROSpect®
- FibroTest®
- Enhanced Liver Fibrosis (ELF)®
- Hepamet Fibrosis Score®
- FibroMeter®
- NIS2+TM®
- NIS4®

Imaging-Based Biomarkers

Measures liver stiffness, corresponding to fibrosis

- FibroScan®/vibration-controlled transient elastography (VCTE)
- Shear wave elastography (SWE)
- Magnetic resonance elastography (MRE)
AGA Clinical Practice Update on Role of Noninvasive Biomarkers for MASLD²

Best Practice Advice Statements

- NITs aid risk assessment in diagnosing MASLD.
- FIB-4 < 1.3 may be useful to exclude advanced fibrosis in initial stratification.
- Combining NITs is preferred for staging MASLD if FIB-4 > 1.3.
- Following NIT guidelines reduces discordant results and risks of additional testing.
- Contextual interpretation and clinical data enhance positive predictive value of NITs.
- Indeterminate or discordant NIT results may prompt consideration of liver biopsy for clarification.
- NIT results may help monitor MASLD progression or regression for informed clinical decisions.
- For patients with MASLD with advanced fibrosis (F3/F4), NITs may prompt end-stage liver complication surveillance. Serial monitoring with various techniques is recommended for longitudinal clinical assessment.

AGA Key Recommendations⁵

Screening and Diagnostic Evaluation of MASLD Using NITs

- **Primary Suspicion**
  - Clinical suspicion for MASLD met
  - Primary assessment
  - Exclude alternative causes

- **Fibrosis Risk Stratification**
  - Prioritize FIB-4 assessment with awareness of limitations
  - Determine diabetes status and metabolic risk factors
  - Sequential testing if high metabolic risk

- **NITs for Advanced Fibrosis**
  - Serial monitoring (prefer imaging-based biomarkers)
  - Consider liver biopsy for discordant NITs
  - Clinical management on stage of disease
The Emerging Role of Liquid Biopsy in the Diagnosis and Management of CRC

David Lieberman, MD, AGAF

Colorectal cancer (CRC) is the third most common cancer in the United States, and early detection and monitoring are crucial for improving patient outcomes. Liquid biopsy (LB) is a revolutionary approach that may offer a non-invasive way to diagnose and manage CRC. The history of LB for CRC reflects a progression from early attempts to detect biomarkers in blood to the current era of precise genetic analysis using circulating tumor deoxyribonucleic acid (ctDNA) and analyzed with next-generation sequencing. The technology has significantly improved over time, leading to the potential for integration into clinical practice and to provide more personalized and effective CRC management.

LB offers several potential advantages for CRC screening compared to traditional non-invasive screening with a stool sample, or invasive screening with colonoscopy. A blood test that could identify high-risk individuals who need colonoscopy is exciting, because it is possible that adherence to screening would be improved with LB. However, there are many challenges. Reduction of CRC mortality or incidence will depend on the ability of the test to accurately detect individuals with early-stage cancer or precancerous advanced polyps. It is not clear if the biology of such lesions would result in an adequate signal in blood if the lesion were not invasive. Test performance also depends on completion of colonoscopy if individuals have an abnormal LB. Testing methods, cost consideration, and clinical validation of performance will need to be addressed. As the technology advances, the role of LB in CRC screening will likely evolve and expand.

The American Cancer Society CRC Estimates for 2024

- **106,590** new colon cancer cases
- **46,220** new rectal cancer cases
- **53,010** deaths from CRC

The lifetime risk of developing CRC:

- **1 in 23** Men
- **1 in 25** Women

1 in 3 adults aged 50 to 75 aren’t adhering to screening recommendations.
## FDA-Approved Liquid Biopsy Tests

<table>
<thead>
<tr>
<th>Name</th>
<th>Approval Year</th>
<th>Indication</th>
<th>Purpose</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Search® Circulating Tumor Cell (CTC) test</td>
<td>2007</td>
<td>Patients with metastatic CRC</td>
<td>Assesses and monitors prognosis. Tests blood to identify, isolate, and enumerate CTCs</td>
<td>First approved LB for enumerating CTCs</td>
</tr>
<tr>
<td>Epi proColon® Epigenomics</td>
<td>2016</td>
<td>Average-risk patients who opt out of traditional screening for CRC</td>
<td>Detects Septin 9 methylated DNA in plasma</td>
<td>First approved LB for cancer-related single gene changes</td>
</tr>
<tr>
<td>Guardant360® CDx</td>
<td>2020</td>
<td>Those with solid CRC tumors, but not blood cancers</td>
<td>Tests blood for multiple cancer-related genetic changes</td>
<td>First approved LB for detecting multiple cancer-related genetic changes</td>
</tr>
<tr>
<td>FoundationOne Liquid CDx</td>
<td>2020</td>
<td>A companion diagnostic to detect NTRK fusions in solid CRC tumors</td>
<td>Identifies those who may benefit from larotrectinib (FDA approval, 2018)</td>
<td>Only approved LB that analyzes 300+ genes</td>
</tr>
<tr>
<td>→ Expanded indication</td>
<td>2023</td>
<td>A companion diagnostic for encorafenib + cetuximab for patients with BRAF V600E-mutated metastatic CRC</td>
<td>Tests blood for ctDNA</td>
<td></td>
</tr>
</tbody>
</table>

## LB Benefits and Limitations

### Potential benefits in CRC screening and cancer management

1. Non-invasiveness and convenience could increase patient compliance for screening
2. May help identify a high-risk individual who should receive a colonoscopy
3. Can help tailor personalized and effective treatment plans based on genetic mutations or CRC biomarkers
4. Provides real-time data about the tumor’s genetic profile and treatment response
5. Can predict relapses and metastases
6. Detects minimal residual disease

### Limitations

1. Less accurate than other CRC screening tests for detection of early stage CRC or pre-cancerous advanced polyps
2. Could be less cost-effective for population-based screening compared to traditional methods based on the operating characteristics of the tests
3. Not as sensitive or specific as tissue biopsy or colonoscopy for detecting and characterizing genetics of CRC
4. Can’t provide information about the specific location or extent of the primary tumor or metastases
5. Availability of reliable biomarkers is still limited
6. Currently lacking validation and standardization across labs
Complementary and alternative therapies are gaining interest in the gastrointestinal (GI) community. Up to 27% of adults in the United States and Canada report using cannabis for medical reasons, and up to 39% of patients with inflammatory bowel disease (IBD) report past use for symptom management. Significant questions and challenges still remain surrounding the use of cannabis in GI disorders, including its varied legalization status globally.

Cannabinoids can be broken down into endocannabinoids (naturally occurring substances within the body) such as 2-arachidonoylglycerol (2-AG) and anandamide (AEA), which act within the body at the cannabinoid receptors (CB) CB1 and CB2. There are also plant-based cannabinoids (phytocannabinoids) that include the most commonly known cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). In addition, there are synthetic cannabinoids (manmade molecules that resemble THC or CBD), and synthetic receptor antagonists and agonists (manmade molecules that act directly at the cannabinoid receptors).

Studies have assessed cannabinoid use in many GI conditions—most notably IBD and irritable bowel syndrome (IBS)—however, medical marijuana use has only been approved in some states for Crohn’s disease or ulcerative colitis. In patients with IBS, there have been conflicting results, with a recent clinical trial of a synthetic CB2 agonist showing no significant change in abdominal pain scores. In patients with IBD, results are also varied, with some trials showing improvement in clinical measures but not endoscopic remission. These varied results could be due to differences in the formulation of cannabinoids studied and routes of administration.

While the endocannabinoid system is of high interest within the GI community due to its therapeutic potential, many challenges remain, such as legalization, widely varied compounds and doses of active ingredients, and a lack of large, high-quality randomized studies. More research is needed to delineate the exact mechanism to best interact with the endocannabinoid system, and what GI disease states might be most affected.

Marijuana Legalization in the United States

The recreational use of cannabis is illegal in most countries outside of the United States and Canada, with some moving toward decriminalization and medical marijuana legalization.

CBD oil can be made with or without THC. This map refers to CBD oil with THC. CBD oil with THC is illegal in states marked as “Fully illegal.” All statuses are subject to state limits and CBD oil may be legal only up to 0.5% THC or marijuana may be legal only up to 1 ounce.
Cannabinoid Treatment in IBS and IBD\textsuperscript{9,10,13,14}

\textbf{CB\textsubscript{2} Receptor Agonist for IBS}

Although the weekly changes in average abdominal pain scores\textsuperscript{2} were similar across study groups, CBD use showed significant improvement in a subgroup of patients who had moderate-to-severe pain at baseline.

\textbf{Change from Baseline AAPS}

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>CB\textsubscript{2} Agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>-1.7</td>
<td>-2.6</td>
</tr>
<tr>
<td>9</td>
<td>-1.8</td>
<td>-2.9</td>
</tr>
<tr>
<td>10</td>
<td>-1.8</td>
<td>-3.3</td>
</tr>
<tr>
<td>11</td>
<td>-1.9</td>
<td>-3.6</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>-3.7</td>
</tr>
</tbody>
</table>

\textsuperscript{2}AAPS, Average Abdominal Pain Score; Scale ranges from 0 to 10 where higher numbers represent worse pain. IBS-C, IBS with constipation; IBS-D, IBS with diarrhea

\textbf{50 mg CBD Chewing Gum for IBS}

\textbf{Change in Abdominal Pain Scores\textsuperscript{4}}

<table>
<thead>
<tr>
<th>CBD</th>
<th>-0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

\textsuperscript{4}Visual analog scale device with subjective pain faces and a 0-10 scale was used for abdominal pain score.

\textbf{Meta-Analysis Data for IBD}

- \textbf{Clinical remission:} Cannabinoids not effective (relative risk, 1.56) (0.99-2.46)
- \textbf{Abdominal pain:} 68%-100\% reported symptom relief (in the cannabinoid group)

\textbf{Cannabinoids in IBS:} Some studies have shown that cannabis use may increase risk for development of IBS, and studies on the use of cannabinoids have not shown significant results in reducing IBS symptoms, except in a small moderate-to-severe IBS subgroup.

\textbf{Cannabinoids in IBD:} Clinical symptoms, such as abdominal pain, nausea, diarrhea, poor appetite, and well-being, have been shown to improve in IBD, but studies have also used varied cannabinoid formulations. No change in inflammatory biomarkers has been observed.
Risks Involved in Cannabinoid Use\textsuperscript{11,15-17}

**Biological Effects:**
- Dizziness, headaches, and sedation
- Change in lung function
- Increased heart rate/arrhythmia risk
- Delayed gastric emptying
- Increased nausea and vomiting
- Decreased sperm count and delayed ovulation

**Logistical Considerations:**
- Legal, travel, and employment implications
- Drug interactions
- Exacerbation of underlying anxiety and depression
- Risk for substance use
- Lack of health care team knowledge
- Patient hesitance to disclose use

Cannabis hyperemesis syndrome (CHS) is also a consequence of cannabis use. CHS is characterized by episodic vomiting, where stopping cannabis use improves symptoms.
AI and Machine Learning in IBD: Promising Applications and Remaining Challenges

Shirley Cohen-Mekelburg, MD, MS

Nearly 1 in 100 Americans have inflammatory bowel disease (IBD), with up to 56,000 new cases being diagnosed each year. IBD is a complex disease with a myriad of presentations, possible treatment approaches, and patient outcomes. Artificial intelligence (AI)—a field of technology which began in the 1950s—refers to the ability of computers to learn and perform tasks that would have typically required human intelligence, while “machine learning” refers to the development of the algorithms that help AI learn patterns from data. The goal in many industries, including health care, is for AI to aid in and improve decision-making. Applications of AI including machine learning already greatly influence the oncology space, aiding in risk assessment, early diagnosis, prognosis, and treatment decision-making.

Although extensive progress in AI has been made since the turn of the century, several limitations remain. Poor-quality data sets may lead to inaccurate predictions, and it is difficult to generalize data sets to minority populations. In health care, clinicians must also understand and be able to interpret the algorithms in order to trust and apply them in practice. Lastly, and importantly, there are ethical concerns regarding patient privacy in data collection.

Potential Applications in IBD

- **IBD Pathogenesis**: Better understand how genetics, environment, and lifestyle contribute to development of IBD
- **Diagnosis and Disease Classification**: Less variation in recognition and interpretation of laboratory testing results, imaging, endoscopic examination, and histology
- **Prediction of Treatment Response**: Limits need for drug monitoring tests, which can be expensive, time-consuming, and inconsistent. Helps determine upfront therapy and who should continue long-term therapy or switch treatment

**Latest Research**

Between 2018 and 2021, there was a 68% increase in published studies of machine learning techniques within IBD-related AI applications.

- **Diagnosis**: Differentiating patients from controls
- **Disease severity**: Predicting IBD activity or complications
- **Disease course**: Examining relapse, remission, and surgery classifiers
- **Other**: Including disease subtype, treatment response, disease risk, patient clustering, medication adherence, medication metabolites, and patient selection
Evolution of AI Research in IBD

<table>
<thead>
<tr>
<th>Area of Focus</th>
<th>2010</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies using multiple types of data</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>Studies focused on treatment response</td>
<td>24%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Studies focused on classification and disease course</td>
<td>12%</td>
<td>&gt;35%</td>
</tr>
</tbody>
</table>

What Do Clinicians Need to Know Right Now?

- Clinical expertise is still necessary to help interpret findings and detect nonrepresentative data, biased results, and poor generalization.
- While variation in IBD practice is common, AI-enhanced decision support has the potential to reduce variability in treatment decisions and improve patient care.

Limitations in AI Applications for IBD

1. Poor-quality data or lack of availability
   - Results in inaccurate algorithms, poor decision-making
2. Disproportionate representation in data samples
   - Creates algorithms that are trained based on specific demographics, which are not generalizable
3. Difficult to explain or interpret algorithms
   - Compromises clinician trust in AI and confidence applying technology into practice
4. Collection of patient data to build algorithms
   - Leads to ethical concerns about protecting patient privacy
5. Complexity of integrating multiple data sets from various sources
   - Makes standardization of data difficult and inhibits seamless integration and analysis
Simulation-Based Training in Endoscopy: Benefits and Challenges
Richa Shukla, MD

The methodologies used to train medical students and professionals are constantly evolving; centuries of studying anatomy with models and figurines—and then practicing on real patients—are now being reexamined in light of emerging technology. Simulation-based training offers a new, seemingly “risk-free” approach to learning because trainees can practice procedures in safe, realistic, patient-free environments. Early mistakes can be made with minimal consequence, training can be tailored to include highly specific clinical scenarios, and the evolving technology helps us accomplish these goals in extremely realistic simulations.1-3 The COVID-19 pandemic further escalated the need for advanced training to be available virtually and helped to shape what these types of programs should look like moving forward.4

As with every new piece of technology, some limitations still need to be addressed. Cost is the first one that comes to mind. While the long-term cost vs benefit debate is not yet settled, the upfront expense is substantial and immediately makes simulation-based training less accessible. The good news is that subsequent costs, such as those for software updates and upgrades, may be much lower. We are also at the mercy of possible technical issues and malfunctions, and the transferability of skills learned virtually into real-life practice may vary from person to person. Nevertheless, many promising elements make simulation-based training an exciting development for preparing the next generation of endoscopists.

Types of Simulation-Based Training in GI Endoscopy1-3

**Mannequins**
- Immediate benefit: Decreases training time
- Long-term benefit: Reduces staff costs and increases learning opportunities
- Challenge: Lacks authenticity and realism; relatively costly

**Virtual Reality**
- Immediate benefit: 30% decrease in procedure time; Adaptable; Portable
- Long-term benefit: Decreases complications, pain ratings, recovery time, and costs
- Challenge: Technology is constantly becoming outdated

**Augmented Reality**
- Immediate benefit: Resembles a real-life surgical experience
- Long-term benefit: Improves efficiencies for inexperienced clinicians
- Challenge: Cannot replace the mentor/mentee experience
Improving Health Care Quality: Simulation-Based Training\textsuperscript{2-4}

Best Practices
- Deliberate practice
- Goal-directed feedback
- Contextual learning
- Innovative education design

Top Benefits
- Provides a low-risk environment
- Prepares trainee for complex tasks and increases competency
- Identifies gaps and opportunities for improvement
- Enhances nonclinical skills (eg, decision-making, leadership, and crisis management)
- Increases patient safety

Gaps in Training
While the implementation of simulation-based training has grown significantly in the 21st century, the COVID-19 pandemic was an unprecedented event that highlighted some remaining areas of unmet need.

Results of the COVID-19 Lockdown
- Skill deterioration
  - In the absence of traditional in-person practice, simulation-based training can help both professionals and students maintain important daily skills.
- Need for crisis-related training
  - Simulation-based training can help health care professionals better prepare for less common, but highly critical scenarios.

Financial Implications\textsuperscript{3,5,6}

Individual simulators cost upwards of \$60,000 to \$100,000.

Costs increase exponentially when funding a full simulation training laboratory.

However, maintenance of these training labs should be cost-efficient once up and running.

Projected forecast for the global health care augmented and virtual reality market.

\$20.76 billion by 2032
Fluid Management in Acute Pancreatitis
Jorge D. Machicado, MD, MPH

Acute pancreatitis is marked by inflammation of the pancreas, potentially leading to organ failure and pancreatic necrosis. Early management relies heavily on intravenous (IV) fluid resuscitation. Initiating fluid resuscitation at an early stage can enhance pancreatic perfusion and maintain adequate systemic circulation, reducing the risk of pancreatic necrosis, hypovolemic shock, and organ failure.¹

Recently, a series of randomized controlled trials have provided a clearer understanding of the type and rate of fluid administration that is the most beneficial for patients with acute pancreatitis.²⁻⁴ The approach to managing fluids in cases of acute pancreatitis may vary depending on the severity of the condition and individual patient factors. Fluids should be prescribed considering their composition (type of fluid), dosing (rate of administration), goals, potential risks, and contraindications.²⁻³ Close monitoring and assessment are essential components of effective fluid management of acute pancreatitis.²

Phases of Fluid Therapy⁵

An international working group has proposed a conceptual model with 4 distinct dynamic phases that can be applied to acute pancreatitis.

1. Rescue
   Rapid infusion of fluid boluses is given right away to correct hypovolemia.

2. Optimization
   Fluid infusion is titrated to optimize tissue perfusion and minimize volume overload (24-72 hours).

3. Stabilization
   Patient is euolemic and maintenance fluids are used for replacement of normal fluid losses.

4. De-escalation
   Fluids are discontinued, and a negative fluid balance (output greater than intake) is promoted as needed.
Rate of Fluid Administration

WATERFALL was a recent multinational, open-label, randomized controlled trial comparing early weight-based aggressive vs nonaggressive fluid resuscitation in patients with acute pancreatitis. This landmark study has helped clarify the question of the optimal rate of fluid administration in acute pancreatitis.

**744 patients** were planned to be randomized and assigned to aggressive (20 mL/kg bolus, followed by 3 mL/kg/h) or moderate (1.5 mL/kg/h, with a bolus of 10 mL/kg only if hypovolemia was present) fluid resuscitation protocols.

**Primary end point.** Detect a difference in the development of moderately severe or severe acute pancreatitis.

**Safety end point.** Evaluate fluid overload based on symptoms, physical signs, or imaging evidence of hypervolemia.

IV fluids should be initiated at a moderate rate within 2 hours after the acute pancreatitis diagnosis is made.

The study was terminated after first interim analysis of 249 patients.

There was **no significant difference** in incidence in moderately severe (MS) or severe acute (SA) pancreatitis by fluid rate:

<table>
<thead>
<tr>
<th>Fluid rate</th>
<th>Aggressive</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of MS or SA pancreatitis</td>
<td>22.1% (P = .32)</td>
<td>17.3%</td>
</tr>
</tbody>
</table>

However, fluid overload was **2.85x greater** with an aggressive vs moderate rate of resuscitation:

<table>
<thead>
<tr>
<th>Fluid rate</th>
<th>Aggressive</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of fluid overload</td>
<td>20.5% (P = .004)</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

**Conclusion**

- **Moderate fluid rate** is safer than aggressive fluid resuscitation, with similar efficacy.

**Moderate fluid rate** (1.5 mL/kg/h) is recommended for patients with **acute pancreatitis** of any severity.

**Fluid boluses of 10 mL/kg** over 1 to 2 hours are recommended for patients with **hypovolemia**.
**Fluid Types**

**Crystalloids or colloids?** In severe acute pancreatitis in 1 RCT of patients with severe acute pancreatitis, crystalloids showed:

- **Lower rates** of adverse events and organ failure
- **Similar survival**

**LR or NS?** In 4 RCTs (n=248), LR has shown to:

- **Reduce risk of ICU admissions** (RR, 0.42; 95% CI, 0.20-0.89)
- **Shorten hospital stay** (mean difference, -1.10; 95% CI, -1.92 to -0.28)

CI, confidence interval; LR, lactated ringer; NS, normal saline; RCT, randomized controlled trial; RR, risk ratio

**Assessing Fluid Volume Status**

**Fluid resuscitation** should be guided by specific goals

- Maintaining adequate blood pressure, urine output (>0.5 mL/kg/h)
- Normalizing hematocrit and electrolyte levels

**Continuous monitoring** is essential to assess fluid status and response to treatment

- Physical exam
- Vital signs
- Urine output
- Laboratory values (hematocrit, blood urea nitrogen, creatinine, electrolytes)

Objective volume assessments should be performed **frequently during the first 24 hours**, and at least every 24 hours to detect or correct any fluid excess or deficits.

**Fluid Overload**

**Diagnosis**

**Common indicators:**
- Dyspnea
- Peripheral edema
- Pulmonary rales
- Increased jugular venous pressure or hepatojugular reflux
- Pulmonary congestion on chest x-ray
- Oxygen saturation < 92%

**If fluid overload is detected:**

- ✔ Decrease or stop fluids.
- ✔ Some patients may require diuretics.

**If severe fluid overload:**

- ✔ Some patients may need mechanical ventilation and/or hemofiltration.
Beyond the Western World

The Changing Face of IBD: Beyond EoE


The Changing Face of IBD: Beyond the Western World


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The Role of Noninvasive Biomarkers: Evaluation and Management of MASLD


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