Microscopic Colitis Foundation

Newsletter Archive

Wayne's Blog

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Researchers Are Closing in on BAM

by Wayne Persky

A study from the University of Cambridge has identified a previously overlooked gut hormone, insulin-like peptide 5 (INSL5), as a key driver of chronic diarrhea, particularly in patients with undiagnosed bile acid malabsorption (BAM) and irritable bowel syndrome with diarrhea (IBS-D). This discovery could transform both the diagnosis and treatment of chronic diarrhea, which is often misclassified and mismanaged.

Published in Gut, and summarized by Science Daily, the study reveals that INSL5 is triggered by bile acids in the colon, leading to a potent laxative response (Bannon et al., 2025; University of Cambridge, 2025, July 29).[1,2] The research not only explains a biological mechanism behind diarrhea-predominant IBS, but also suggests that a diagnostic blood test and targeted treatment options may soon become reality.

What is INSL5?

INSL5 is a hormone secreted by specialized L-cells in the distal (lower) colon and rectum. Until now, its physiological role in humans has been poorly understood. This new research reveals that INSL5 is rapidly released when bile acids, particularly taurocholic acid (TCA), reach the rectum, acting like a “poison detector” to quickly purge irritants by way of diarrhea.

Bile acids aren’t meant to be in the colon — they’re an irritant and toxic to the microbiome. INSL5 likely evolved to get rid of these substances quickly,” explains Dr. Chris Bannon, the study’s lead author.

> **ISNL5 promotes diarrhea.**

> **And is triggered by bile acids in colon.**

BAM tends to dominate bowel function if it's present.

- BAM affects about 1 in 100 people, but it's frequently misdiagnosed as IBS-D.
- Up to 40% of MC patients with chronic diarrhea that doesn't respond to proper diet changes, and patients diagnosed with IBS-D may actually have undiagnosed BAM, leading to ineffective treatment.
- BAM occurs when bile acids are not reabsorbed in the small intestine and spill into the colon, triggering watery, urgent diarrhea (that may mimic the secretory diarrhea associated with MC).

To make the discovery,

Researchers used a novel antibody-based immunoassay (developed with Eli Lilly) to measure INSL5 levels in:

- Healthy controls
- BAM patients
- IBS-D patients
- Volunteers given a bile acid enema

They found that:

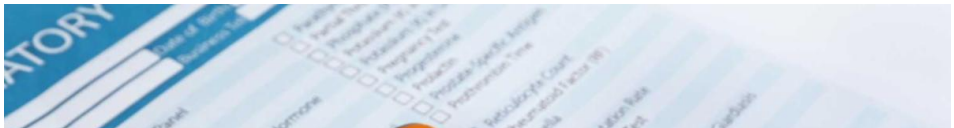
- Healthy people had very low or undetectable INSL5 levels (less than 100 pg/mL).
- BAM patients had markedly elevated INSL5, which correlated with stool looseness.
- IBS-D patients showed elevated INSL5 in approximately 40% of cases, many of whom were misdiagnosed or untreated.

Ondansetron may be a treatment

The team also analyzed patients from an earlier trial involving ondansetron, a common anti-nausea drug that has been shown to reduce diarrhea in some IBS-D patients. They found that:

- Ondansetron appears to block the effects of INSL5 (based on animal models).
- IBS-D patients with elevated INSL5 levels responded significantly better to ondansetron therapy than those without.

“This gives us a new biomarker for identifying which IBS-D patients may benefit most from ondansetron, or new drugs that target this hormone pathway,” said Dr. Bannon.



A blood test may be on the horizon.

INSL5 levels in the blood could soon become a biomarker for bile acid-driven diarrhea, replacing current indirect or unavailable tests for BAM. This could lead to faster, more accurate diagnosis,especially in cases where patients are misdiagnosed with vague labels like “IBS.”

Many MC patients may eventually benefit.

As is usually the case, MC wasn't even considered in this study, but we've learned long ago that roughly 40% of MC patients whose diarrhea doesn't respond to proper diet changes probably have BAM. To date, we've had to guess at the cause of the problem, and the only treatment we've had available has been a bile acid sequestrant. Soon, we may have a blood test to confirm BAM, and much better treatment options.

This discovery should revolutionize the way BAM is treated.

Prior to this, most treatments focused on reducing the amount of bile acids that reach the colon. Probably the first line treatment involves the use of bile acid sequestrants, and that's the approach we normally recommended at the Microscopic Colitis Foundation when someone was unable to coax their MC into remission by making all the proper diet changes and giving it adequate time to work.

Note that 3 types of BAM have been described.

Type 1 BAM is associated with ileal disease or intestinal resection.
This type occurs when there is damage to or removal of the terminal ileum, the part of the small intestine responsible for reabsorbing bile acids. The damaged or missing ileum cannot reabsorb bile acids, so they overflow into the colon, leading to irritation and diarrhea. This can occur due to:

- Crohn’s disease affecting the terminal ileum
- MC (which commonly causes more inflammation in the ileum, than in the colon).
- Ileal resection (surgical removal, often due to IBD or cancer)
- Radiation enteritis (damage from pelvic/abdominal radiation)

Type 2 BAM is idiopathic.

The exact cause is unknown, and there is no identifiable bowel disease or surgery. This is common in people previously diagnosed with IBS-D (diarrhea-predominant irritable bowel syndrome), As noted above, previous studies have shown that up to 40% of these patients actually have BAM.

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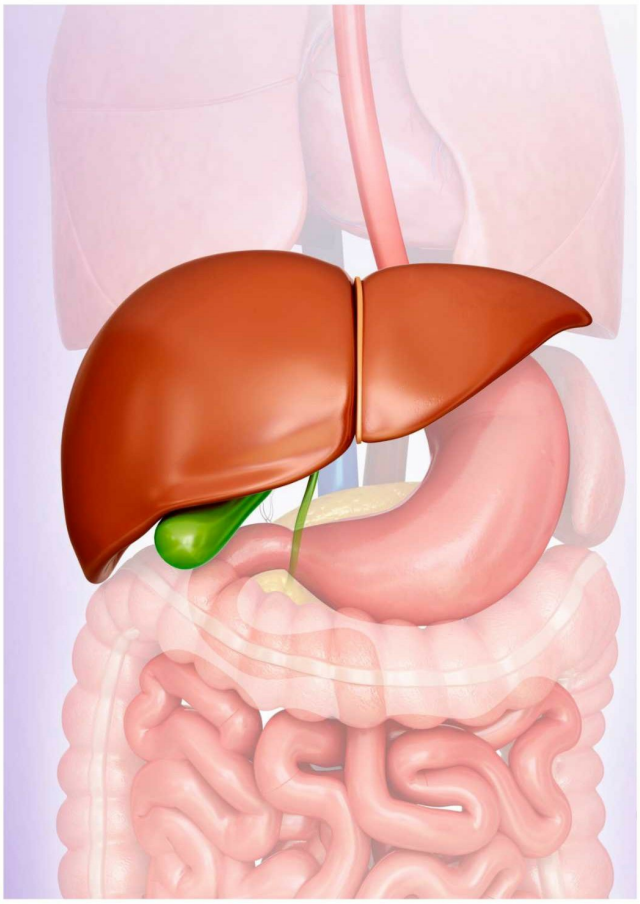
BAM is under-recognized and often confused with IBS.



Possible causes:

- Impaired signaling in the feedback loop between the ileum and liver (for example, decreased FGF19, a hormone that suppresses bile acid production)
- Abnormal bile acid synthesis regulation in the liver
- Often overlooked and underdiagnosed due to the lack of structural damage that can be seen through an endoscope.

Type 3 BAM is secondary to other gastrointestinal (GI) disorders. This is usually caused by BAM that arises in association with other G.I. diseases that do not directly involve the ileum, such as:

- Celiac disease
- Pancreatic insufficiency
- Cholecystectomy (gallbladder removal)
- Small intestinal bacterial overgrowth (SIBO)
- MC (both lymphocytic colitis and collagenous colitis)

Note that although MC is claimed to be a disease of the colon, published research shows that in most MC patients, the ileum is highly inflamed, so arguably, MC should also be added to this list, justifying its appearance on listings for both type 1 and type 3 BAM.

Treatments currently available:

1. Bile acid sequestrants:

Cholestyramine (Questran, Prevalite)

- Most commonly prescribed
- Powdered resin taken before meals
- Often effective, but can be difficult to tolerate due to taste and GI side effects (bloating, constipation, nausea)

Colesevelam (Welchol)

- Tablet form (easier for many patients)
- Better tolerated than cholestyramine
- Off-label use for BAM but increasingly preferred

Colestipol (Colestid)

- Older bile acid binder; less commonly used now
- Powder or tablet

Approximately 2 out of 3 patients respond well to bile acid sequestrants. Those with Type 1 BAM (secondary to ileal disease or resection) often respond better than idiopathic or Type 2 BAM.

2. Low-fat diet:

- Reduces bile acid secretion and may help control symptoms.
- Often recommended in conjunction with medication, especially in patients with mild or borderline BAM.

3. Ondansetron (Zofran)

- Originally an anti-nausea drug (5-HT3 receptor antagonist).
- New research (the 2025 Cambridge study mentioned above) shows ondansetron may be effective in BAM patients with elevated INSL5 hormone levels.
- May reduce diarrhea and improve stool consistency in BAM or IBS-D patients.

4 Probiotics and gut targeted therapies

- Limited but growing research supports modulating the microbiome in BAM patients, especially those with overlapping IBS or dysbiosis.
- Lactobacillus rhamnosus GG and Saccharomyces boulardii have shown some promise.

5. Investigational or emerging therapies

- FXR agonists (for example, obeticholic acid) are being studied for their ability to regulate bile acid synthesis.
- INSL5-targeted therapies may be on the horizon based on recent hormone research from Cambridge (2025), especially for patients with bile acid–triggered diarrhea who don't respond to sequestrants.

Some of the challenges and considerations include the following issues:

- BAM is under-recognized.
- Many patients are misdiagnosed with IBS-D.
- Bile acid sequestrants can interfere with absorption of fat-soluble vitamins and medications, therefore the timing of dosing is important.
- BAM can coexist with MC, celiac disease, or any other IBD, requiring a tailored treatment approach.

Reliable diagnosis is currently a problem (at least in the U.S.)

The SeHCAT scan (used mainly in the UK and EU) can confirm BAM, but in the U.S., diagnosis is often clinical, based on symptom response to bile acid sequestrants or serum C4 and fecal bile acid measurements, which tend to boil down to mostly a trial and error approach. Hopefully, that will change, in the not-too-distant future.

References

1. Bannon, C. A., Walters, J. R. F., Wu, T., Kay, R. G., Punnoose, A., Spiller, R. C., . . . Gribble, F. M. (2025). Insulin-like peptide 5 is released in response to bile acid in the rectum and is associated with diarrhoea severity in patients with bile acid diarrhoea. Gut, [Published Online First] Retrieved from https://gut.bmj.com/content/early/2025/07/23/gutjnl-2025-33539
2. University of Cambridge. (2925, July 29). This gut hormone could explain 40% of IBS-D cases—and lead to a cure. Science Daily, Retrieved from https://www.sciencedaily.com/releases/2025/07/250729001208.htm

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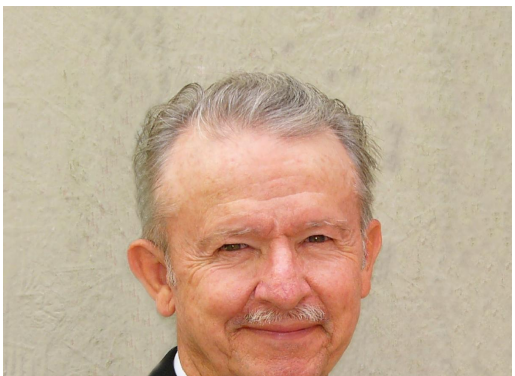

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