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Posted Date: 8 September 2025

doi: 10.20944/preprints202509.0576.v2

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Hypothesis

Barrier Repair in ME/CFS: Lessons from Prototype Diseases

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is marked by heterogeneous symptom clusters and only partial or short-lived responses to interventions. While gut involvement has been implicated in ME/CFS, it has not been proven to be the root cause, nor have symptoms been consistently responsive to treatment. **Methods:** We analyze prototype illnesses with known gut barrier dysfunctions from the duodenum to the colon to identify similarities and symptoms that are direct results of barrier dysfunction. In particular, we assess what can be learned from these prototype diseases that depends not on pathogenesis, but on barrier breakdown and metabolite leakage. **Results:** Prototype diseases showed consistent involvement of pore pathways, frequent histamine leakage, and parallel treatment responses, despite differing in pathogenesis or region involved.

Keywords: ME/CFS; Myalgic Encephalomyelitis; gut barrier; paracellular permeability; proximal colon; microbial metabolites; patient clustering; leak pathways; claudin pores

1. Introduction

Dr. Anouk W. Vaes and collaborators at CIRO performed one of the largest systematic surveys of ME/CFS symptom patterns, applying clustering methods to patient-reported outcomes to identify recurring constellations of symptoms [1]. The study demonstrated that ME/CFS can be partitioned into multiple reproducible subgroups, each with distinct symptom burdens and emphases. While this clustering approach highlighted the extent of heterogeneity in ME/CFS, it also left unresolved why certain symptoms consistently co-occur and what biological processes might underlie those patterns.

We analyzed symptom severity patterns and, like many before us, found that symptoms were strongly correlated. Several stood out as plausibly gut-related, prompting us to ask whether symptoms could localize patient clusters to a specific gut region but they were unable to. Instead, these symptoms tracked closely with overall post-exertional malaise (PEM) severity. This suggested a broader gut barrier problem rather than a localized one. We therefore turned to prototype diseases with established barrier dysfunction, asking whether they could help clarify how barrier breakdown itself contributes to illness — in other words, to distinguish root disease mechanisms from the direct consequences of barrier breach.

2. Paracellular Pathways

To explain our findings, we first review paracellular pathways. Two major types are recognized in the gut epithelium: claudin pores and the leak pathway[2,3].

2.1. Characteristics

Each pathway can be characterized by:

- Size range of molecules transported
- Charge selectivity (cations, anions, or both)
- Potential for activation independent of overt inflammation

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- Mechanisms of closure or deactivation

In normal physiology, claudin pores provide regulated passage of small, charged molecules, while the leak pathway accommodates larger, less selective solutes during epithelial turnover. When dysregulated, these same routes can become conduits for gut-derived metabolites.

- **Anion-selective pores** favor small, negatively charged solutes such as lactate and organic acids.
- **Cation-selective pores** favor small, positively charged solutes such as histamine and polyamines.
- **Leak pathway** is less selective, admitting medium- to large-sized molecules during periods of inflammation or cytoskeletal stress[4].

Unlike claudin pores, leak pathways do not create high-flux channels for ions. Their permeability is passive and limited to existing gradients, so they allow entry of ions and small solutes, but less efficiently than pore pathways.

Chronic dysbiosis may alter not only pore signaling but also pore distribution. Over time, the number and type of pores in each gut segment can shift, and clinical improvement may require months of epithelial remodeling before a stable, healthy population of channels is restored.

Table 1. Summary of Gut Paracellular Pathways.

Pathway	Size Range	Activation	Closure/Deactivation
Leak	Up to a few kDa	Inflammatory / cytoskeletal stress	Requires resolution of inflammation / cytoskeletal reset
Anion Pore	Small molecules (< 6–8 Å)	Claudin isoform–specific signals	Rapid closure via tight junction proteins
Cation Pore	Small molecules (< 6–8 Å)	Claudin isoform–specific signals	Rapid closure via tight junction proteins

These pathways are not mutually exclusive—simultaneous opening of leak and pore routes provides an explanation for the partial effects of interventions that address only one pathway[2] as well as symptom complexity.

2.2. Pathway Interventions

Leak and pore pathways differ in how they respond to interventions.

Leak: Experimental physiology shows that leak openings are driven primarily by inflammatory and cytoskeletal processes[4]. They can close rapidly once inflammation resolves but do not respond to ion-channel or charge-selective signals.

Pore: In contrast, pore-mediated transport is regulated by claudin-specific, charge-selective signaling[2,3]. Pores open and close independently of inflammation, often with rapid gating in response to ionic or metabolic cues.

In practice, interventions that resolve inflammation target the leak pathway most directly, whereas interventions that alter charge-selective signaling primarily affect pores.

3. Prototype Diseases

Diseases were selected based on the following criteria:

- Gut-centric in origin
- Documented evidence of:
  - Barrier dysfunction
  - Metabolites exported from the lumen
  - Symptom associations for each metabolite
  - Clear identification of unique metabolites (e.g., ethanol) unlikely to be universal
- Some symptom overlap with the Vaes patient clusters beyond fatigue and brain fog

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- Broad coverage across the gastrointestinal tract

All of the prototype diseases release metabolites that, once absorbed, can trigger host cytokine expression. These metabolites may contribute to common ME/CFS symptoms such as fatigue and brain fog, in addition to their metabolite-specific effects. We present the final list of diseases below:

Table 2. Disease and Gut Region Association

Disease	Gut Region
Celiac disease	Duodenum / Jejunum
SIBO / D-lactic acidosis	Duodenum / Jejunum
Crohn's ileitis	Ileum
IBS-D	Proximal Colon
Microscopic / Inflammatory colitis	Colon (diffuse)
Ulcerative colitis (UC)	Distal Colon
Clostridioides difficile colitis	Distal Colon

3.1. Metabolites, Symptoms, and Paths

The set of metabolites documented in our prototype illnesses is surprisingly small — roughly a dozen. Here we list each one, the prototype illness associated with it, the path by which it is thought to reach the extra-luminal space, and the symptoms reported in that disease context.

Fatigue or brain fog are included only when directly attributed to the metabolite itself, rather than as secondary consequences of cytokine activation.

Path definitions:

- **Diffusion:** Metabolite passes freely through the gut epithelium without requiring barrier dysfunction.
- **Overproduction:** Metabolite is produced in excess in the gut (e.g., by enterochromaffin cells) and enters circulation independently of barrier disruption.
- **Pore:** Metabolite crosses via small, selective paracellular channels formed by tight junctions.
- **Leak:** Metabolite crosses via larger, non-selective paracellular defects associated with tight junction breakdown.

Table 3. Metabolites, Paths and Illnesses

Metabolite	Illnesses	Path	Documented Symptoms in Those Illnesses	Citation
Acetaldehyde	SIBO / D-lactic acidosis	Diffusion	Cognitive impairment, dizziness	[5,6]
Bile acids	Crohn's ileitis, IBS-D	Pore	Diarrhea/urgency, abdominal pain, sleep/circadian disturbance, weight change	[7,8]
D-lactate	SIBO / D-lactic acidosis	Pore	Neurocognitive dysfunction, dizziness, fatigue*	[9,10]
Ethanol	SIBO / D-lactic acidosis	Diffusion	Dizziness, alcohol intolerance, malaise	[11,12]
Gliadin peptides	Celiac disease	Leak	Food intolerance, brain fog	[13,14]

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Metabolite	Illnesses	Path	Documented Symptoms in Those Illnesses	Citation
Histamine	Celiac disease, Crohn's ileitis, IBS-D, Microscopic colitis, SIBO	Pore	Flushing, headaches, abdominal pain, dizziness, fatigue	[15,16]
H_2S (diffused)	Ulcerative colitis, Clostridioides difficile colitis	Diffusion	Nausea, toxic-feeling flares, headaches	[17,18]
Indoxyl sulfate	Ulcerative colitis, Clostridioides difficile colitis	Pore	Chemical/odor sensitivity, vascular headaches	[19,20]
p-Cresol	Ulcerative colitis, Clostridioides difficile colitis	Pore	Chemical/odor sensitivity, vascular headaches	[21,22]
SCFAs (e.g., butyrate, acetate, propionate)	IBS-D, Microscopic colitis	Over produced/pore	Bloating, abdominal pain, malaise	[23,24]
Serotonin	Celiac disease, IBS-D	Over produced	Sleep disturbance, mood lability, GI motility issues	[25,26]

* Emerging [https://biosignaling.biomedcentral.com/articles/10.1186/s12964-025-02132-z]

Not listed in this table are cytokines, which do not cross the gut barrier but are immune moderated causes for fatigue, malaise, fever/flu-like symptoms, and inflammatory flares

4. Disease, Metabolite, Path Summary

When summarized by pathway and metabolite, our prototype diseases share two broad associations: pore-mediated leakage and histamine involvement.

We infer the pathway by the metabolite and based on this all of these diseases would involve significant pore activity, and most — with the exception of the two colitis forms — are associated with histamine leakage.

Table 4. Disease, region and pathways

Disease	Gut Region	Pathways Used for Metabolite Leakage
Celiac disease	Duodenum / Jejunum	Pore (histamine), Leak (gliadin peptides), Overproduction of Serotonin
SIBO / D-lactic acidosis	Duodenum / Jejunum	Pore (D-lactate,histamine), diffusion (Ethanol, Acetaldehyde)
Crohn's ileitis	Ileum	Pore (bile acids, histamine)
IBS-D	Proximal Colon	Pore (SCFAs, histamine, serotonin, bile acids), Overproduction of serotonin
Microscopic / Inflammatory colitis	Colon (diffuse)	Pore (SCFAs, histamine), Leak
Ulcerative colitis (UC)	Distal Colon	Pore (indoxyl sulfate, p-cresol), diffusion (H_2S)
Clostridioides difficile colitis	Distal Colon	Pore* (secondary bile acids, p-cresol, indoxyl sulfate); Diffusion (H_2S)

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* Toxin-mediated epithelial injury (TcdA/TcdB) disrupts the barrier; classification reflects metabolite passage routes but the initiating damage is toxin-driven, not a canonical tight-junction pathway change.

5. Interventions

Looking across the prototypes, a consistent pattern emerges in the interventions that fail versus those that succeed (see Appendix A).

1. **Inflammation-only strategies do not resolve the root problem**
   - Steroids, 5-ASA, biologics, or antihistamines alone can suppress cytokines or dampen symptoms, but they do not prevent metabolite leakage across the barrier.
   - This explains relapses in UC, Crohn's disease, and microscopic colitis, as well as only partial symptom relief in CFS-type patients.
2. **Symptom-only drugs fail**
   - Agents such as loperamide in IBS-D, antidiarrheals in SIBO, or painkillers in colitis provide temporary relief but leave the underlying export of metabolites unaddressed.
   - As a result, the disease process continues despite symptomatic improvement.
3. **Barrier repair and metabolite-targeted interventions show the greatest promise**
   - Remove the offending metabolite (e.g., gluten-free diet in celiac).
   - Reduce metabolite production (e.g., antibiotics in SIBO, low-FODMAP diet in IBS-D).
   - Bind or block metabolites (e.g., bile acid sequestrants in Crohn's disease, IBS-D, microscopic colitis).
   - Normalize barrier function (e.g., larazotide in celiac, though Phase 3 trials failed).
   - Restore metabolite ecology (e.g., fecal microbiota transplantation in *C. difficile* and UC).

These pattenrs mimic what we see for ME/CFS, and other diseases.

6. Discussion

If ME/CFS gut involvement parallels the patterns observed in our prototype diseases, then effective interventional trials should prioritize two strategies: normalizing pore pathway function and reducing histamine activity.

Moreover, the relatively small number of distinct metabolites identified across prototypes suggests that metabolite leakage in ME/CFS may also be limited in scope, even when multiple gut regions are involved. This constraint may help explain why patients exhibit overlapping symptom clusters despite heterogeneous overall presentations.

7. Conclusions

We have presented a survey of prototype diseases that shed light on ME/CFS interventions and potentially other chronic illnesses. Although these diseases differ in pathogenesis, they share two key features: gut barrier disruption and metabolite leakage. Their treatment responses are also broadly shared with ME/CFS, in that anti-inflammatory agents fail to provide durable benefit or yield only limited improvements.

Acknowledgments: This paper could not exist without the foundational work of Dr. Anouk W. Vaes and her colleagues at CIRO, whose clustering study and publicly available cluster summary data provided the basis for our analysis. We are deeply grateful for their contribution to the field. Dr. Vaes had no role in the writing of this paper, and all errors or misinterpretations are the responsibility of the author.

Author Contributions: Erik K. Squires conceived the study, performed the analysis, and wrote the manuscript. This work presents an original investigative method and resulting framework which were both developed and first reported by the author in this preprint.

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Conflicts of Interest: The author declares no competing interests.

Funding: This work received no external funding.

Informed Consent Statement: his study reanalyzed publicly available trial reports and published symptom cluster data (Vaes 2023). No new patient data were collected.

Appendix A. Appendix A: Barrier-targeted interventions by prototype

Appendix A.1.

Celiac disease (Duodenum/Jejunum)

Barrier pathway focus	Successful / promising	Failed / limited
Leak (gliadin peptides); Pore (histamine)	Gluten-free diet (GFD): normalizes permeability and resolves symptoms in adherent patients[1]. Larazotide (TJ modulator): Phase 2 RCTs showed symptom benefit during gluten challenge[2].	Larazotide Phase 3: discontinued for lack of efficacy[3]. Anti-inflammatories/biologics: not effective for routine CeD, do not address barrier leak[4].

SIBO / D-lactic acidosis (Duodenum/Jejunum)

Barrier pathway focus	Successful / promising	Failed / limited
Pore (D-lactate, histamine); Diffusion (ethanol, acetaldehyde)	Antibiotics such as rifaximin and metronidazole reduce bacterial overgrowth and improve symptoms[5]. Dietary carbohydrate restriction (low-FODMAP, low simple sugars) reduces fermentation and metabolite load[6]. Some probiotics reduce D-lactate producers, though evidence is mixed[7].	Anti-inflammatories do not address metabolite production or permeability[8]. Symptomatic drugs (antidiarrheals) do not address underlying leakage[9].

Crohn's ileitis (Ileum)

1 Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. *ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease*. Am J Gastroenterol. 2013.
2 Leffler DA, et al. *A randomized, double-blind study of larazotide acetate to prevent the activation of celiac disease during gluten challenge*. Gastroenterology. 2012.
3 Innovate Biopharmaceuticals press release; Larazotide Phase 3 discontinued, 2022.
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5 Pimentel M, et al. *Rifaximin therapy for patients with irritable bowel syndrome without constipation*. N Engl J Med. 2011.
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9 Grace E, et al. *Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis*. Clin Gastroenterol Hepatol. 2013.

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Barrier pathway focus	Successful / promising	Failed / limited
Pore (bile acids, histamine)	Bile-acid sequestrants (cholestyramine, colesevelam) reduce bile-acid diarrhea in ileal Crohn's and resection patients[10]. Nutritional therapy (exclusive enteral nutrition) improves barrier integrity and reduces inflammation[11].	Antihistamines (H1/H2) alone have not shown consistent benefit in IBD[12]. Anti-TNF and other biologics reduce inflammation but do not directly normalize bile-acid–driven barrier leakage[13].

Barrier pathway focus	Successful / promising	Failed / limited
Pore (SCFAs, histamine, bile acids); **Overproduction** (serotonin)	**Rifaximin** improves global symptoms and bloating in IBS-D[14][15]. **Bile-acid sequestrants** (e.g., colesevelam/cholestyramine) help IBS-D subsets with bile-acid excess[16]. **Low-FODMAP diet** reduces fermentation load → symptom improvement[17][18]. **5-HT3 antagonists** (e.g., alosetron; ondansetron in smaller trials) reduce urgency/diarrhea[19][20].	**Anti-inflammatory/biologic therapies** (cytokine-targeted) are not effective for IBS-D[21]. **Symptom-only meds** (e.g., loperamide) don't address metabolite production or permeability[22].

IBS-D (Proximal Colon)

10 Fernandez-Banares F, et al. *Cholestyramine in the treatment of bile acid malabsorption in Crohn's disease*. Gastroenterology. 1991.
11 Ruemmele FM, et al. *Enteral nutrition as primary therapy for Crohn's disease: impact on mucosal healing and barrier function*. Gut. 2004.
12 Sander LE, et al. *Histamine H4 receptor antagonism reduces inflammation in murine colitis but has not translated to clinical efficacy in IBD*. Inflamm Bowel Dis. 2015.
13 Peyrin-Biroulet L, et al. *Anti-TNF therapy in Crohn's disease: long-term outcomes*. J Crohns Colitis. 2011.
14 Pimentel M, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med. 2011.
15 Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021.
16 Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021.
17 Halmos EP, et al. A diet low in FODMAPs reduces symptoms of IBS: a randomized controlled trial. Gastroenterology. 2014.
18 Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021.
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Barrier pathway focus	Successful / promising	Failed / limited
Pore (SCFAs, histamine, bile acids); Overproduction (serotonin)	**Rifaximin** improves global symptoms and bloating in IBS-D[2324]. **Bile-acid sequestrants** (e.g., colesevelam, cholestyramine) help subsets with bile-acid excess[25]. **Low-FODMAP diet** reduces fermentation load and improves symptoms[2627]. **5-HT3 antagonists** (e.g., alosetron; ondansetron in smaller trials) reduce urgency and diarrhea[2829].	**Anti-inflammatory/biologic therapies** (cytokine-targeted) are not effective in IBS-D[30]. **Symptom-only meds** (e.g., loperamide) do not address metabolite production or permeability[31].

Microscopic / Inflammatory colitis (Colon, diffuse)

Barrier pathway focus	Successful / promising	Failed / limited
Pore (SCFAs, histamine); Leak	**Budesonide** is first-line therapy and effective at inducing remission, though relapse is common after withdrawal[3233]. **Bile-acid sequestrants** are helpful in patients with bile-acid malabsorption, with ~2/3 showing benefit[3435].	**Mesalamine and other anti-inflammatories** show inconsistent or minimal efficacy[36]. **Probiotics** have not shown consistent benefit[37].

Ulcerative colitis (Distal Colon)

23 Pimentel M, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med. 2011.
24 Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021.
25 Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021.
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Barrier pathway focus	Successful / promising	Failed / limited
Pore (indoxyl sulfate, p-cresol); Diffusion (H_2S)	5-ASA (mesalamine) and steroids induce remission by reducing inflammation, though they do not prevent metabolite leakage[38][39]. Dietary modulation (e.g., low-sulfur diets) may reduce H_2S burden, limited supportive evidence[40]. FMT shows benefit in some patients, likely by restoring bile-acid and SCFA metabolism[41].	Biologics (anti-TNF, anti-integrin) are effective for inflammation but do not address barrier dysfunction or metabolite leakage[42]. Barrier-directed agents (e.g., larazotide) have not been tested in UC.

Clostridioides difficile colitis (Distal Colon)

Barrier pathway focus	Successful / promising	Failed / limited
Pore* (secondary bile acids, p-cresol, indoxyl sulfate); Diffusion (H_2S)	**FMT** is highly effective for recurrent CDI, restoring secondary bile acid metabolism that inhibits C. difficile germination[43][44]. **Standard antibiotics** (vancomycin, fidaxomicin) resolve acute infection but do not restore barrier or metabolite balance[45]. **Bezlotoxumab** (anti-toxin B monoclonal) reduces recurrence in high-risk patients[46].	**Anti-inflammatories** provide no benefit as they do not address toxin or metabolite leakage[47]. Recurrence rates remain high with antibiotics alone.

* Toxin-mediated epithelial injury (TcdA/TcdB) disrupts the barrier; classification reflects metabolite passage routes but the initiating damage is toxin-driven, not classic tight junction dysfunction.

38 Sutherland LR, et al. Mesalazine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2000.
39 Truelove SC, et al. Cortisone in ulcerative colitis: final report on a therapeutic trial. BMJ. 1955.
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