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Review article: small intestinal bacterial overgrowth, bile acid malabsorption and gluten intolerance as possible causes of chronic watery diarrhoea

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SUMMARY

Background
Chronic watery diarrhoea is one of the most common symptoms prompting GI evaluation. Recently, new diagnostic considerations have emerged as possible factors in chronic diarrhoea.

Aim
To review available data regarding diagnosis and treatment of chronic diarrhoea with an emphasis on bacterial overgrowth and bile acid malabsorption.

Methods
A systematic search of the English language literature of chronic diarrhoea was performed focused on three possible aetiologies of diarrhoea: small intestinal bacterial overgrowth (SIBO), idiopathic bile salt malabsorption (IBAM), gluten responsive enteropathy.

Results
Recent studies suggest that SIBO and bile acid malabsorption may have been underestimated as possible causes of chronic watery diarrhoea. Gluten intolerance with negative coeliac serology is a contentious possible cause of watery diarrhoea, but requires further research before acceptance as an entity.

Conclusion
In patients with otherwise unexplained chronic watery diarrhoea, small intestinal bacterial overgrowth and bile salt malabsorption should be considered and investigated.

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INTRODUCTION

This review will focus on the clinical evaluation and differential diagnosis of chronic watery diarrhoeas. They commonly present considerable diagnostic challenges for clinicians.

A systematic search for relevant literature was performed through Pubmed and using as key words, chronic diarrhoea, small intestine bacterial, hydrogen breath test, irritable bowel syndrome, bile salt induced diarrhoea, SeHCAT, coeliac disease, gluten sensitive enteropathy.

FUNDAMENTALS OF A DIARRHOEA WORK-UP

Donowitz, *et al.* concluded that a specific diagnosis could be reached in approximately 90% of cases of chronic watery diarrhoea, although he estimated that 30% of those patients would be labelled functional diarrhoea.[1] A detailed history, physical exam and appropriate work-up should be performed to search for other causes of diarrhoea, i.e. 'the rule/out work-up' before the final diagnosis of functional diarrhoea or IBS is made.

It is important to consider the role of diet. Poorly absorbed carbohydrates (lactose, but also fructose and sorbitol and excessive ingestion of coffee (i.e. Starbucks ^{R} diarrhoea) may be contributing factors.[2] Medications should also be considered as a possible cause.[3] Haemoglobin A1C, thyroid function tests and coeliac serology should be measured. Colonosocopy is appropriate to diagnose microscopic colitis, a common aetiology of chronic watery diarrhoea. A normal faecal calprotectin or lactoferrin makes the likelihood of an occult inflammatory process less likely. However, recent reports suggest that it may also be increased in microscopic colitis.[4]

A timed stool collection for 48–72 h may be a logistic challenge for both patient and physician, but this can provide invaluable information that can guide further diagnostic studies. By measuring stool electrolytes and osmolarity, one can calculate an osmotic gap i.e. osmolarity that is not accounted for by the measured electrolytes. A significant gap (>50 mosm) implies an osmotic diarrhoea, whereas a minimal gap is consistent with a secretory diarrhoea. Osmotic diarrhoeas are associated with the ingestion of a poorly absorbed solute such as sorbitol. Recent evidence suggests that dietary fructose, fructans (fructo-oligosaccharides), may also be significant causes of osmotic diarrhoea.[5, 6] Identification and elimination of the offending agent generally eliminates the diarrhoea. Perhaps more important than the calculation of an osmotic gap is the stool weight itself. A stool weight of >1 kg/day (volume>1 L/day) generally indicates secretory diarrhoea, particularly if the diarrhoea continues with similar volume after cessation of oral intake. Intravenous fluid replacement should be provided while this is assessed. It is our experience that approximately 20% of patients with a complaint of chronic diarrhoea will have normal stool weights; this finding clearly shapes further diagnostic studies.

TRENDS IN DIAGNOSIS OF CHRONIC WATERY DIARRHOEA

Over the last several decades, novel insights into the possible aetiologies of chronic diarrhoea have considerably expanded our differential diagnosis. An elegant study by Fordtran's group in 1980 in a very select group of patients estimated that perhaps a third of patients with chronic diarrhoea may be laxative abusers.[7] This then led to many work ups searching for occult laxative use. Although this is always a diagnostic consideration, the incidence in a general GI referral practice appears to be much less 30%.

With the advent of radioimmunoassays for a series of neuropeptides, the consideration of a secretory diarrhoea driven by a specific hormone such as VIP became an attractive diagnosis. Although these are now commonly ordered tests, their utility in the initial stages of a diarrhoea evaluation is yet to be demonstrated. About 50% of the patients with chronic diarrhoea could have false positive results; in some patients, the abnormal value is as high as is seen with peptides-secreting tumours.[8] Even with tumours secreting these peptides, testing for VIP can probably only identify the tumours with liver metastasis.[9] This suggests that random testing is probably not warranted.

Laxative abuse and neuroendocrine tumours will account for only a small percentage of cases of chronic diarrhoea. Over the last several years, two new diagnostic considerations have emerged as possible factors in chronic diarrhoea: small intestinal bacterial overgrowth and idiopathic bile salt malabsorption. These are not new diagnoses *per se*, but changing patterns of either diagnostic testing or diagnostic criteria have led to more frequent identification of these as

the aetiology for chronic diarrhoeas. These novel explanations for chronic diarrhoea are intriguing and may well expand both our understanding of the pathophysiology of diarrhoea and our therapeutic options. It is unclear how well they will stand the test of time. We will review these with a specific focus on the accuracy of diagnostic tests, specificity of therapeutic options and plausibility of proposed pathophysiology.

SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

Small intestinal bacterial overgrowth has increasingly been implicated as a major aetiological factor in IBS, primarily diarrhoea predominant IBS (D-IBS).[10] Bacterial overgrowth in the distal small intestine may be diagnosed by an abnormal hydrogen breath test (HBT) in many of patients with IBS. Normalization of breath tests and improvement of symptoms after a course of antibiotics tend to support the SIBO-IBS connection. However, several studies failed to confirm the frequent diagnosis of SIBO in IBS patients.[11–13]

Small intestine bacterial overgrowth (SIBO) is a condition generally associated with anatomic or motility abnormalities. Symptoms related to SIBO include gas bloating, diarrhoea, weight loss, malabsorption and anaemia. The diagnostic gold standard has been the quantitative culture of luminal fluid from small intestine. However, this test is rarely performed in clinical practice. And indeed, if SIBO/IBS is due to distal small intestine bacterial overgrowth, jejunal cultures may not be diagnostic.

Because of the disadvantage of cultures, various breath tests have been proposed as non-invasive tests for SIBO.[14] C-Dxylose breath test has been most rigorously tested, but it is available only in selected academic centres. Thus almost by default, HBTs, using glucose or lactulose, are the most commonly used tests for SIBO. The reported sensitivity and specificity for HBT varied from 27 to 93% and from 30% to 86% respectively for glucose HBT; and from 17% to 89% and from 44% to 100% respectively for lactulose HBT compared to small bowel cultures from proximal small bowel.[14–20] The wide range in sensitivity and specificity suggested potential problems with the reliability of these tests and the potential pitfalls in directing clinical decision on them.

Many factors may affect the accuracy of HBT. For example, carbohydrate malabsorption, the oral bacterial flora or a high fibre diet can result in false positive tests. A false negative result may also occur either because of prior antibiotic treatment or because of the lack of H_2 producing bacteria. Variables in the test protocols, such as dosage of carbohydrate administered, method of collection, the amplitude of increase in H_2 considered as positive test can all affect the results of HBT.

Rapid intestinal transit is the most important confounding variable in applying HBTs to the diagnosis of SIBO. As lactulose is a non-absorbable disaccharide, it passes through the small intestine into the colon normally, where it is quickly metabolized. Thus, conventionally, an H_2 signal from lactulose represents OCTT. A double peak pattern (early for bacterial metabolism in the small intestine and late for OCTT) has been proposed to be diagnostic for SIBO, but even this putatively classic pattern may not be entirely specific.[18, 21]

Given the uncertainties in utilizing breath tests for the diagnosis of SIBO, it is critical to establish rigorous criteria to confirm the SIBO/IBS linkage. This requires (1) clearly distinguishing SIBO from OCTT and (2) identifying clear differences in breath tests in IBS compared to normals. In the absence of a double peak, a positive lactulose BT has been defined as an increase in H_2 within 90 to 180 min in various studies.[22–24] However, OCTT in normals may be as short as 60 min or less measured by barium meal.[25] Lactulose itself may accelerate small bowel transit.[26] Clearly, rapid transit may occur in patients with diarrhoea of multiple aetiologies. Relatively early increases in breath hydrogen after lactulose ingestion (<90 min) may have a greater specificity for overgrowth.[27] A rise in breath H_2 within 20 min after lactulose ingestion probably, but not always, indicates overgrowth.

A combined breath test with a nuclear medicine intestinal transit scan, which provides an independent measure of OCTT, can improve the diagnostic accuracy of HBTs for overgrowth. As shown in Figure 1, without a simultaneous intestinal transit scan, the HBT pattern is suggestive of small bowel bacterial overgrowth. However, the early rise of hydrogen is due to the rapid intestinal transit and colonic bacterial metabolism of the test sugar. A combined HBT/nuclear transit scan test improved the specificity of a lactulose HBT from 70 to 100%, although the sensitivity was still limited.[17] A similar approach with glucose as the test sugar has demonstrated the ability to delineate rapid transit from overgrowth, improving the clinical reliability of a breath test with an alternate sugar.[28]

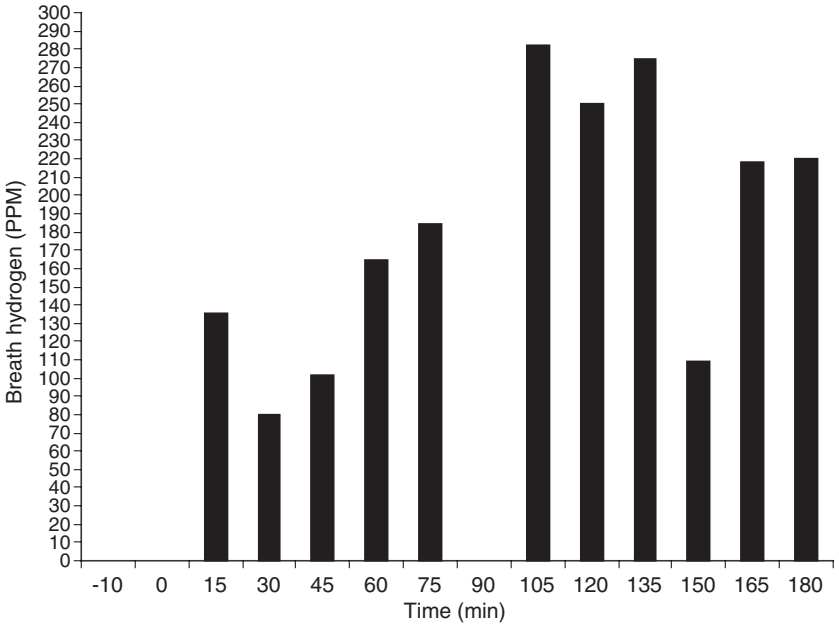

Figure 1. Lactulose H_2 Breath Test in an individual with chronic diarrhoea. The test was markedly positive by 15 min. A simultaneous nuclear medicine intestinal transit scan demonstrated tracer in the caecum at 12 min. Methane levels were zero throughout the test. (The 90 min collection was lost). Apparent SIBO by HBT alone, in fact, when combined with a transit scan, led to a diagnosis of rapid transit.

It is unclear what might predispose an individual with IBS to SIBO. There is no clear consensus regarding motility changes in IBS. Different studies have found either similar motility in patients with dIBS and cIBS,[22, 29] or alternatively, reduced frequency of house keeping waves and rapid transit in dIBS.[30, 31] While altered motility may lead to SIBO, the reverse is also a consideration: SIBO may lead to changes in small bowel motility.[32]

Antibiotic therapy is the current standard for SIBO. Several studies have suggested a benefit for rifaximin in IBS associated SIBO as shown in Table 1. Other antibiotics such as neomycin, and metranidazole also show some benefits in patients with IBS and SIBO (Table 1). Improvement in bloating and global symptoms but not necessarily diarrhoea has been observed.[37, 41] Interestingly, the rifaximin dose used in these trials is considerably higher than that used to treat traveller's diarrhoea. In contrast, classic SIBO associated with GI surgery, scleroderma, or small bowel diverticulosis treated with norfloxacin, amoxicillin, tetracycline or metronidazole demonstrated a much higher symptom response rate including significant improvement in diarrhoea.[42–44]

A recent study comparing lactulose HBT in IBS patients and normal controls found that the lactulose breath test does not differentiate between these two groups.[45] This emphasizes the concern about the specificity of breath tests for diagnosis of SIBO in IBS. Although SIBO may occur in some patients with IBS, it is likely that many of the positive breath tests are due to rapid small bowel transit or limitations of breath test itself. Similarly, while some individuals clearly benefit from high dose rifaximin or other antibiotics, further studies are needed to clarify whether the improvement is indeed from the treatment of SIBO, or, alternatively, from changes in colonic flora. It may be revealing to determine whether antibiotic treatment eliminates a specific signal for SIBO or whether, alternatively, it reduces the overall H_2 signal, i.e. the *AUC* (area under the curve) produced by a carbohydrate challenge.

Spiegel, *et al.* recently proposed an alternative hypothesis of the relationship between SIBO and IBS. Because individuals with IBS are more likely to have concomitant upper GI symptoms, they are more likely to be on proton pump inhibitors. There are some data to suggest that PPIs can promote SIBO. If this is indeed the case, then a finding of a positive breath test or jejunal culture in patients with d-IBS may actually represent an epiphenomenon, rather than a true causal relationship. Clearly, future studies in this arena will need to control or stratify for acid-suppressive therapy.[46] Thus, if there is a significant clinical suspicion for overgrowth as a factor in diarrhoea, it seems prudent, at this point, to consider the role of PPIs and to obtain a breath test combined with a transit scan to improve the diagnostic accuracy.

Classically, SIBO causes malabsorption by bacterial deconjugation of bile salts and by a bacterial 'steal' syndrome in which luminal nutrients are captured and metabolized before normal absorption can occur.

Table 1. Antibiotic treatment in patients with SIBO for both IBS and predisposing conditions

Authors (Reference)	Diagnosis	*N*	Treatment	Breath test normalization	Symptom improvement
Scarpellini *et al.*[33]	IBS and SIBO	80	Rifaximin	58% for 1.2 g/day 80% FOR 1.6 g/day	NR
DiStefano *et al.*[34]	Functional bowel disorder	34	Rifaximin or activated charcoal	NR	Rifaximin reduce overall symptoms severity ($P < 0.02$)
Sharara *et al.*[35]	Bloating and flatulence	63	Rifaximin	NR	43% improvement in rifaximin group 23% improvement in placebo group ($P = 0.03$)
Yang *et al.*[36]	SIBO and IBS	84	Rifaximin	56%	69% of patient
Pimentel *et al.*[37]	IBS and SIBO	87	Rifaximin	NR	Global improvement ($P < 0.02$), sustained for 10 weeks post treatment
Pimentel *et al.*[38]	IBS and SIBO	55	Neomycin	20%	35% improvement in rifaximin group 11.4% improvement in placebo group ($P < 0.05$)
Pimentel *et al.*[39]	IBS and SIBO	19	Neomycin	NR	37% global symptoms improvement vs. 5% for placebo ($P < 0.001$)
Pimentel *et al.*[40]	IBS and SIBO	47	Mix of neomycin, ciprofloxin, flagyl, or doxycycline	53%	Eliminate IBS in 48% of subjects

However, the clinical spectrum of SIBO may be shifting.[47] Watery diarrhoea associated with SIBO may be seen more frequently, perhaps because of a multifactoral process involving low grade mucosal inflammation, intestinal motility changes, increased secretion caused by deconjugated bile salt, hydroxylated fatty acids, and bacterial enterotoxins.[32] SIBO may be a common cause of chronic diarrhoea in elderly patients.[48, 49]

IBAM: BILE SALT INDUCED DIARRHOEA

Bile acid malabsorption (BAM) is a recognized cause of chronic diarrhoea. It is unclear, however, how often idiopathic bile acid malabsorption (IBAM) is a factor in diarrhoea of uncertain aetiology. In normal subjects, more than 95% of the bile acids secreted by the liver are reabsorbed in the small bowel before reaching the caecum. Three types of bile malabsorption have been recognized as listed in Table 2.

Table 2. Three types of bile acid malabsorption

	Category	Related conditions
Type 1	Related to ileal dysfunction	Ileal resection, disease of ileum, or bypass
Type 2	Idiopathic	No structural defect, ? transporter defect
Type 3	Miscellaneous	Cholecystectomy, peptic ulcer surgery/vagotomy, coeliac disease, diabetes mellitus, pancreatitis

In type I BAM, malabsorbed dihydroxy bile acids, such as chenodeoxycholic acid and deoxycholic acid, inhibit colonic sodium absorption and stimulate chloride secretion, causing diarrhoea.[50] Malabsorbed bile salt may also increase colonic permeability, thereby providing another mechanism for diarrhoea.

Chronic diarrhoea post cholecystectomy, an example of type III BAM, is common, occurring in 10–20% of cases. The pathophysiology remains unclear. As bile acids may reside in the gut for a greater proportion of the enterohepatic circulation, it is possible that bacterial dehydroxylation increases diarrheogenic bile acids.

(Hoffman AF, personal communication). Alternatively, altered motility may contribute to watery diarrhoea. The migrating motor complex may sweep the intestinal content including bile acids that rapidly passes through the ileum into the colon, leading to BAM type III. However, it remains unclear how frequently BAM actually occurs post cholecystectomy.[51, 52] Colonic transit time has been shown to be decreased after cholecystectomy.[53]

The pathogenesis of IBAM is controversial. A frequently offered hypothesis is a defect in the ileal bile acid transport system. A mutation in the ileal sodium-dependent bile salt transporter gene has been identified rarely in a paediatric population,[54] but the mutation has not been found in adults with presumed IBAM.[55, 56] Increased small bowel and colonic motility has also been suggested as possible aetiology of IBAM.[57] In trying to sort out cause and effect, it is important to recognize that induced diarrhoea in normal controls can also cause mild bile acid malabsorption.[58]

Specific diagnostic tests for BAM are limited. Direct measurement of faecal bile acid output involves complicated research methods not applicable to clinical use. SeHCAT (selenium-75-homocholic acid taurine) is a radio labelled synthesized cholic acid. It is absorbed from the gut and secreted into the bile at the same rate as cholic acid. SeHCAT retention is used clinically for the diagnosis of BAM. Unfortunately, it is not available in the United States. IBAM was initially reported as a rare cause of chronic diarrhoea. After the introduction of SeHCAT as a diagnostic tool, IBAM was reported more frequently in chronic diarrhoea as shown in Table 3.

Table 3. Abnormal SeHCAT test reported in chronic watery diarrhoea

Author (Reference)	Publication year	% of patients with abnormal test
Williams *et al.*[59]	1991	37
Sciarretta *et al.*[60]	1994	60
Fernández-Bañares *et al.*[61]	2001	75
Wildt *et al.*[62]	2003	56
Muller *et al.*[63]	2004	42
Fernández-Bañares *et al.*[64]	2007	45.2

The diagnosis of IBAM depends, quite obviously, on the criteria used; there appear to be a wide variation of normal and abnormal ranges in different studies. Although parameters of total body retention, abdominal retention and gall-bladder retention study have all been proposed, several studies document high false positive and false negative rates using faecal SeHCAT, 3 alpha-hydroxy bile acid, or combination of the two, when compared to type 1 BAM standards such as patients with ileal resections.[65–69] Given that BAM may be a manifestation of diarrhoea instead of the cause, it is important to recognize that SeHCAT cannot delineate primary and secondary BAM related to diarrhoea. In fact, it has been suggested that SeHCAT test is of 'no value' in the routine evaluation of chronic diarrhoea.[70] Although that may be an extremely critical view, it is important to recognize the limitations of the test.

Response to empirical treatment with cholestyramine may be a simpler diagnostic test. Failure to respond to a therapeutic trial of cholestyramine makes BAM an unlikely cause of diarrhoea. There are no clinical trials comparing dosing schedules of binding resins for BAM. The conventional approach was starting with 4 g cholestyramine or colestipol hs, adding one dose of binder 2 h after breakfast, then 2 h after lunch, then 2 h after dinner for incomplete response. However, if patients respond only to large amount of cholestyramine (more than 12 gm), it is unclear whether this should be considered a positive or a negative test.[59] One must recognize the possibility of a false therapeutic cholestyramine trial because of the well-recognized constipating effect of this drug in normals and patients with others causes of diarrhoea. The true incidence of IBAM remains unknown, but is probably overestimated by both SeHCAT and response to cholestyramine.

GLUTEN RESPONSIVE ENTEROPATHY: THE NEXT NOVEL DIAGNOSIS?

The diagnosis of coeliac disease (CD) traditionally is based on the triad of symptoms, serology and intestinal histology. Over the last decade, it has become clear that CD with positive serological testing and typical histology (Marsh 3) can present with a wider range of symptoms than previously appreciated.[71] However, more recently, several investigators have demonstrated 'gluten responsive symptoms' in the absence of either positive serological testing (negative anti-TTG and negative anti-EMA) or with less severe pathological criteria (Mash 1/Marsh 2) alone.

In a study of 102 patients with diarrhoea predominant IBS with a negative serology for CD, intestinal fluid antibodies for gliadin and TTG were identified in 30%. Significant improvement in diarrhoea and a decrease of intestinal fluid antibody were observed in response to a gluten-free diet.[72]

In another recent study evaluating 62 patients with chronic watery diarrhoea, the diagnosis of gluten-related enteropathy was reached without any testing of coeliac serologies i.e. no antiTTG or anti-endomysical antibody testing was performed.[64] Individuals identified as HLA-DQ2 or HLA-DQ8 positive had small bowel biopsies. Those with Marsh 1/2 lesions (33% of either HLA-DQ2 or HLA-DQ8 positive patients) were placed on a gluten-free diet. Clinical improvement was seen in 83% of these patients. A follow-up study identified a significant number of individuals diagnosed with D-IBS who both had serum IgG markers (as compared to duodenal) for CD; almost two thirds of these individuals responded to a gluten-free diet.[73]

These studies raise interesting questions, suggesting there may be a 'gluten-responsive enteropathy' not meeting the conventional histological or serological criteria for true gluten-sensitive enteropathy that can cause watery diarrhoea. It is becoming well recognized that there may be sero-negative cases of CD that correlate to lesser severity of histological involvement.[64, 72] According to conventional criteria, the diagnosis of coeliac disease can only be firmly established with Marsh 3 lesions. Marsh 1 or 2 lesions are fairly non-specific and may be secondary to many other conditions such as bacterial overgrowth, NSAIDS use, allergic to proteins other than gluten. Because of the technical difficulty and variability to count intraepithelial lymphocytes (IEL), some authorities have concluded that IEL by themselves are 'virtually of no diagnostic value' for the evaluation of coeliac disease.[74]

In our increasingly health and diet conscious society, there has been a proliferation of gluten-free products available in health food stores and even conventional grocery stores. Gluten-free foods are also increasingly available on the internet. Caution is of course required as the symptomatic response to gluten-free diet may be a nonspecific gastrointestinal response to a major dietary change or to the low-residue nature of a gluten-free diet. Whether these diets may benefit a broader segment of the population than previously recognized remains an open question.

At present, it is difficult to translate this expansive definition of gluten responsive disease into a coherent cost effective evaluation of diarrhoea. HLA typing for DQ 2 and DQ8 is expensive and may be positive in 30% of the general population. Positive HLA typing by itself cannot establish a diagnosis of CD. The pitfalls of Marsh 1/2 lesions are well-recognized. There are real costs and challenges involved in a lifelong gluten-free diet. Finally, there are significant implications that come with a diagnosis of CD. Some patients with this broader definition of gluten-responsive disease may well eventually develop more typical CD. The proportion that will is unknown at present. Hopefully, ongoing clinical research will provide a more comprehensive picture.

CONCLUSION

Chronic diarrhoea is a challenging condition to evaluate. A specific diagnosis can be made in most chronic diarrhoea patients after detailed investigation. But, there is considerable uncertainty involved with the accuracy of some diagnostic studies. A response to empirical therapy certainly benefits the patient, but may not necessarily establish a specific diagnosis. Some new and novel diagnostic considerations may expand our differential spectrum, but require critical evaluation.

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