Factors That Affect Prevalence of Small Intestinal Bacterial Overgrowth in Chronic Pancreatitis: A Systematic Review, Meta-Analysis, and Meta-Regression

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OBJECTIVES: Small intestinal bacterial overgrowth (SIBO) can complicate chronic pancreatitis (CP) and interfere with management. Its predisposing factors in CP and treatment response are unknown. In this review, we evaluated factors affecting disease burden.

METHODS: A computerized search of PubMed and EMBASE databases from inception through May 2019 was done for studies correlating SIBO with CP. Studies were screened, and relevant data were extracted and analyzed. Pooled prevalence, odds ratio (OR), and meta-regression were performed using the random effects model as classically described by Borenstein et al. (2009). SIBO's relation to diabetes mellitus (DM), pancreatic exocrine insufficiency (PEI), narcotic use, and proton-pump inhibitor use was investigated. Treatment response was pooled across studies. P value < 0.05 was considered significant.

RESULTS: In 13 studies containing 518 patients with CP, SIBO prevalence was 38.6% (95% confidence interval [CI] 25.5–53.5). OR for SIBO in CP vs controls was 5.58 (95% CI 2.26–13.75). Meta-regression showed that PEI and the diagnostic test used were able to explain 54% and 43% of the variance in SIBO prevalence across studies, respectively. DM and PEI were associated with increased SIBO in CP with OR (2.1, 95% CI 1.2–3.5) and OR (2.5, 95% CI 1.3–4.8), respectively. Symptomatic improvement was reported in 76% of patients after SIBO treatment.

DISCUSSION: SIBO complicates 38% of CP with OR of 5.58 indicating a predisposition for this condition. PEI correlates with SIBO in CP and might play a role in pathophysiology. DM and PEI are associated with increased SIBO in CP. Treatment of SIBO may lead to symptomatic improvement.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A93

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INTRODUCTION
Chronic pancreatitis (CP) is an inflammatory disorder involving injury and scarring of the pancreatic exocrine gland, which can also affect endocrine components. It has a global incidence of 10 per 100,000 population (1). CP results in a variety of signs and symptoms, including abdominal pain, weight loss, bloating, steatorrhea, malabsorption, and diarrhea. CP complications include pancreatic exocrine insufficiency (PEI), postpancreatitis diabetes mellitus (DM), and pancreatic cancer. Management of CP is challenging with multiple modalities targeting symptoms and malnutrition through pain management, pancreatic enzyme replacement therapy (PERT), and, in severe cases, surgery including total pancreatectomy. Despite advancements in CP treatment, 43% of patients do not respond to conventional therapy (2).

Recent evidence suggests that pancreatic exocrine dysfunction is a major determinant of intestinal microbiota (3). Changes in the gut microbial composition have been linked to a wide array of disorders spanning infectious (4), autoimmune (5), functional (6), neoplastic (7), and gastrointestinal (GI) pathologies. Multiple reports have linked CP to microbial dysbiosis, mainly small intestinal bacterial overgrowth (SIBO). SIBO has classically been

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linked to blind-loop–producing GI surgeries; the resulting combination of altered anatomy, altered motility, hypochlorhydria, and exposure to colonic contents creates a favorable environment for bacterial proliferation (8). SIBO is associated with inflammatory bowel disease (9,10), neurological disorders (11,12), celiac disease (13), and irritable bowel syndrome (14). SIBO symptoms include abdominal pain, bloating, diarrhea, and malabsorption, which overlap with CP and make the diagnosis and management of SIBO in CP all the more difficult. Although Capurso et al. (15) showed in 2016 that SIBO affects 36% of patients with CP, we noted a high level of heterogeneity in the reported SIBO prevalence. In addition, their review lacked an analysis of SIBO’s response to treatment or of risk factors for SIBO in CP. Moreover, we found that 3 additional studies (16–18) had been published on this subject since then. Therefore, we performed a comprehensive systematic review and meta-analysis employing rigorous statistical analysis using meta-regression models to explain heterogeneity, determine factors affecting disease prevalence, and response to treatment of SIBO in CP.

METHODS
Eligibility criteria
The primary criterion for eligibility was the availability of data on SIBO incidence in clinically diagnosed CP/PEI. Although confounding factors such as alcohol and narcotic use were often reported, because of sparsity of data, studies that did not statistically account for confounders were included. No restrictions were applied on study design, including CP definition adopted by investigators. Adequate description of diagnostic technique of CP (clinical history, imaging and functional studies) and PEI (stool elastase/fat excretion) was required. Adequate description of diagnostic test description, including substrate dose, test duration, sampling intervals, and positive test criteria; SIBO diagnostic method; method of CP diagnosis; prevalence of DM, alcohol, proton-pump inhibitor (PPI), and narcotic use; surgical history; PERT; control group characteristics; SIBO diagnostic method, to explain heterogeneity, determine factors affecting disease prevalence, and response to treatment of SIBO in CP.

Search technique
A computerized search of the MEDLINE and EMBASE databases from inception to May 2019 was performed. Search terms were as follows: chronic pancreatitis, pancreatic exocrine insufficiency, breath tests, small intestine, bacterial infections, bacterial overgrowth, lactulose hydrogen, glucose hydrogen, and jejunal aspirate. Duplicates were excluded. Abstracts of remaining articles were reviewed. Unrelated articles were excluded. The remaining articles were reviewed in detail for eligibility criteria.

Data extraction
For each study, data were extracted on year published; study design; number of patients/controls; participant age and sex; etiology of CP; method of CP diagnosis; prevalence of DM, alcohol, proton-pump inhibitor (PPI), and narcotic use; surgical history; PERT; control group characteristics; SIBO diagnostic test description, including substrate dose, test duration, sampling intervals, and positive test criteria; SIBO treatment; and treatment outcomes. Finally, SIBO prevalence in both CP and controls was extracted. Study quality was assessed using the Newcastle-Ottawa scale (NOS) for cross-sectional and case-control studies. Cutoff of 6 or higher was considered good quality, whereas <6 was considered poor quality.

Statistical analysis
Pooled prevalence of SIBO in multiple subsets of patients with CP was calculated. Random effects model was used to calculate pooled prevalence estimates with 95% confidence intervals (CIs). Heterogeneity was assessed using the I² measure and the Cochran Q-statistic. Odds ratio (OR) of SIBO in CP compared with controls was calculated based on events/total ratios of both groups. The following stratified analyses were conducted to address sources of heterogeneity and determine factors affecting SIBO prevalence in CP: (i) PEI, (ii) DM, (iii) PERT use, (iv) alcoholic CP, (v) mean age, (vi) SIBO diagnostic method, (vii) surgical history, (viii) study quality per NOS, (ix) PPI use, and (x) narcotic use. Meta-regression was performed as classically described (19) using (i)–(iii) above as covariates in logistic regression models aimed at uncovering correlations between such covariates and SIBO prevalence, which might explain heterogeneity. Publication bias was assessed for using the Begg and Mazumdar test. Statistical analysis was performed using the software programs Comprehensive Meta-Analysis version 3.3.070 (Biostat, Englewood, NJ) and Review Manager (RevMan) version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark).

RESULTS
Our search identified 2,236 references. Initial screening included review of titles to exclude duplicates, and subsequently, abstracts were screened for relevance. A total of 2,192 studies were excluded as duplicates, conference abstracts, or unrelated to the review subject. This resulted in 44 studies that were reviewed in detail, 13 of which met our eligibility criteria. Only 8 studies...
compared SIBO event rates in CP vs controls and were included in the comparative analysis (Figure 1).

Study breakdown
The studies were conducted in 11 countries; 6 European, 2 Asian, 1 South American, and 2 North American. They were published between 1985 and 2019. Twelve studies were published in English, 1 in Russian (20), and 1 in Spanish (21). Ten case-control and 3 cross-sectional studies examining 518 patients with CP and 372 controls were included. Study characteristics are depicted in Table 1. Three studies included CP patients with a history of gastroduodenal or pancreatic surgery (gastrectomy, vagotomy, pancreaticoduodenectomy, and Puestow procedure) (21–23), and 2 of those also included surgical patients in the control group (22,23). Eight studies used glucose hydrogen breath test (GHBT), 4 used lactulose hydrogen BT (LHBT), and 1 used jejunal aspirate culture. Three studies combined breath methane with LHBT/GHBT (16,24,25). Test techniques are listed in Table 2. CP diagnostic method is listed in Table S2 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A93). The individual studies found no association between patient-age, sex, or PEI and SIBO prevalence. Only 2 studies (16,17) found DM and PERT to be more prevalent in SIBO patients. Nine of 13 studies were of high quality on the NOS, and the remaining 4 were considered of poor quality (Table S1, see Supplementary Digital Content 1, http://links.lww.com/CTG/A93). Sensitivity analysis excluding poor-quality studies did not significantly alter analysis results.

Prevalence of SIBO in CP
The studies reported prevalence in a range from 0%–93%. Pooled prevalence of SIBO in CP across the 13 included studies was 38.6% (95% CI 25.5%–53.5%) with considerable heterogeneity ($I^2 = 87\%$) (Figure 2a) compared with 9.9% (95% CI 4.9%–19%) in controls. The studies were subgrouped based on the inclusion of subjects with a GI surgical history. Pooled prevalence was 34.6% (95% CI 20.7%–51.8%) in nonsurgical studies and 54.2% (95% CI 23.3%–82.2%) in surgical ones (Figure 2b). When subgrouping based on the diagnostic test

| Study | Year | Country | Patients (n) | Sex (male %) | Age (yrs) | Alcoholic CP (%) | Narcotic use (%) | DM (%) | Previous surgery (%) | PERT (%) | Controls (n) | Control characteristics |
|-------|------|---------|--------------|-------------|-----------|-----------------|-----------------|--------|---------------------|---------|------------|------------------------|
| Lee et al. (16)a | 2019 | United States | 98 | 50 | μ 51.9 | NR | 33.7 | 25.5 | 44.9 | 0 | 58.2 | None |
| Ní Chonchubhair et al. (17)a | 2018 | Ireland | 35 | 67 | μ 51.7 | 45.3 | 33 | 100 | 45.7 | 0 | 86 | 31 | Healthy |
| Kim et al. (24)a | 2015 | South Korea | 36 | 77.8 | μ 52.3 | 78.9 | 0 | NR | 66.6 | 0 | 52 | 49 | Healthy |
| Therrien et al. (18)a | 2015 | Canada | 31 | 71 | μ 53.8 | 41.9 | NR | NR | 12.9 | 0 | 51.6 | 40 | Healthy |
| Kumar et al. (27)a | 2014 | India | 68 | 70.6 | μ 33.6 | 32.3 | 58.8 | 31.7 | 35 | NR | 66.2 | 74 | Healthy |
| Signoretti et al. (31)a | 2014 | Italy | 43 | 55.8 | μ 54 | 39.5 | NR | 39.5 | 41.8 | 0 | 62.8 | 43 | Unspecific GI Sx |
| Grigor’eva et al. (20) | 2010 | Russia | 102 | 34.3 | μ 55 | NR | NR | 70.6 | NR | 0 | NR | None |
| Mancilla et al. (21)a | 2008 | Chile | 14 | 78.5 | μ 49 | 50 | NR | 100 | 28.5 | 21.4 | 64 | 14 | Healthy |
| Madsen et al. (25) | 2003 | Denmark | 11 | 100 | M 46 | 100 | 54.5 | 100 | 45 | 0 | 90 | 11 | Healthy |
| Trespi and Ferrieri (23)b | 1999 | Italy | 35 | 74.2 | μ 53 | 54.3 | NR | 100 | 14.3 | 31.4 | 100 | 61 | Gastric resection |
| Casellas et al. (22)a | 1998 | Spain | 15 | 73.3 | μ 51 | 73.3 | NR | 100 | 66.6 | 66 | 100 | 39 | Immunodeficient/Gastroduodenal surgery |
| Bang Jørgensen et al. (26) | 1991 | Denmark | 10 | NR | NR | NR | NR | 100 | NR | 0 | 0 | 10 | Healthy |
| Lembcke et al. (59) | 1985 | Germany | 20 | NR | NR | NR | NR | 95 | 40 | 0 | NR | None |

μ, mean; CP, chronic pancreatitis; DM, diabetes mellitus; GI, gastrointestinal; M, median; NR, not reported; PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement therapy; Sx, symptoms.
aIncluded in comparative analysis.
used, pooled prevalence in 8 studies using GHBT was 26.7% (95% CI 18.0%–37.7%) compared with 65.3% (95% CI 38.1%–85.1%) in the 4 studies using LHTB (Figure 2c). The one study using jejunal aspirate cultures showed a prevalence of 50% (26). To further understand the sources of heterogeneity between studies, we performed a meta-regression analysis taking into account covariates such as surgical history of subjects, number of patients with PEI, DM, PERT, alcoholic etiology of CP, age, and diagnostic test used. Only “number of patients with PEI” and “diagnostic test used” were able to explain the observed variance. Meta-regression models of these 2 covariates were able to explain 55% and 43% of the variance in prevalence between the studies, respectively (Figure 3a,b).

A sensitivity analysis excluding studies with surgical patients was performed; 8 studies remained and showed a significant correlation of SIBO prevalence with number of patients with PEI. This model was able to explain 71% of variance (Figure 3c).

**Factors affecting SIBO in CP**

Eight studies evaluated the effect of DM on SIBO in CP and found it was associated with increased SIBO with OR (2.1, 95% CI 1.2–3.5) (Figure 4a). After stratification by the diagnostic test used, DM was found to be associated with increased SIBO in patients tested with GHBT only and not in those tested with LHTB. Four studies evaluated the effect of PEI on SIBO in CP, and it was associated with increased SIBO with OR (2.5, 95% CI 1.3–4.8) (Figure 4b). Further analysis of studies evaluating the effects of PPI, narcotic use, and PERT did not yield significant increase in SIBO (Figure S2A–C, see Supplementary Digital Content 1, http://links.lww.com/CTG/A93).

**SIBO in CP compared with controls**

Eight studies compared the event rate of SIBO in CP with controls and were included in this analysis. The OR for a positive test in CP vs controls was 5.58 (95% CI 2.26–13.75) (I² = 60%) (Figure 5a). Subgroup analysis showed an OR of 16.6 (95% CI 1.33–206.69) (I² = 81%) for SIBO in CP in 3 studies using LHTB, compared with 3.2 (95% CI 1.38–7.42) (I² = 30%) in 5 studies using GHBT (Figure 5b,c). Upon subgrouping based on surgical history, 3 studies using patients with a surgical history showed an OR of 10.86 (95% CI 0.90–131.72) (I² = 79%), whereas 5 studies excluding patients with a surgical history yielded an OR of 4.61 (95% CI 1.67–12.73) (I² = 50%) (Figure 5d,e).

Publication bias was assessed for using 2 funnel plots (Figure S1, see Supplementary Digital Content 1, http://links.lww.com/CTG/A93) and the Begg and Mazumdar test. No publication bias was found.

**Clinical presentation and response to treatment**

All studies except that by Madsen et al. (25) reported symptoms in the SIBO group refractory to PERT. Five studies reported a trial of antibiotics, 3 studies used rifaximin (17,23,27), Casellas et al. (22)
Figure 2. PP of SIBO in CP data: (a) Shows PP across the 12 included studies. (b) Shows PP in studies subgrouped by inclusion of patients with a surgical history concomitant with CP. As indicated by overlap in CI, there was no significant difference between PP in studies which included CP patients with a surgical history and those which excluded surgical patients. (c) Shows PP in studies subgrouped by the diagnostic test used. As indicated by nonoverlap in CI, the use of LHBT results in a significantly higher PP of SIBO in CP than GHBT (\( P < 0.05 \)). CI, confidence interval; CP, chronic pancreatitis; GHBT, glucose hydrogen breath test; LHBT, lactulose hydrogen breath test; PP, pooled prevalence; SIBO, small intestinal bacterial overgrowth.
Figure 3. Meta-regression results for PP analysis: (a) Meta-regression exploring the relationship between the SIBO event rate in CP and number of patients with PEI. As indicated in the accompanying table, correlation was not statistically significant. Despite that, the regression model was able to explain 54% ($R^2$) of between-study variance in PP. (b) Meta-regression exploring the relationship between the SIBO event rate and the diagnostic test used. As indicated in the accompanying table, the correlation was statistically significant. The logistic regression model was able to explain 43% ($R^2$) of between-study variance in PP. (c) Meta-regression exploring the relationship between the SIBO event rate in CP and number of patients with PEI after exclusion of studies with surgical patients. As indicated in the accompanying table, the correlation was statistically significant and able to explain 71% ($R^2$) of between-study variance in PP. $R^2$ calculation: (a) To compute the total variance (of all studies about the grand mean), we run the regression with no covariates. (b) To compute the variance not explained by the model (of all studies about the regression line), we run the regression with the covariates. (c) The difference between these values gives us the variance explained by the model. CP, chronic pancreatitis; GHBT, glucose hydrogen breath test; LHBT, lactulose hydrogen breath test; PEI, pancreatic exocrine insufficiency; PP, pooled prevalence; SIBO, small intestinal bacterial overgrowth.
used doxycycline followed by metronidazole, and Lee et al. (16) used an unspecified antibiotic regimen (Table 3). We pooled the data from these studies to show that 86% of patients treated with rifaximin showed symptomatic improvement compared with 40% of those treated with doxycycline and metronidazole (Figure 6).

**DISCUSSION**

This meta-analysis provides the latest evidence on the association between SIBO and CP. Although SIBO prevalence was highly heterogeneous, it was more likely to be present in patients with CP than controls with an OR of 5.58 (95% CI 2.26–13.75). The type of the diagnostic test used significantly affected SIBO prevalence with LHBT, showing a higher prevalence than GHBT. Studies including patients with a surgical history had higher SIBO prevalence, although this was not statistically significant. We found DM and PEI to be associated with significant increases in SIBO in CP. In addition, we note that PEI correlates with SIBO prevalence and explains 54%–71% of the heterogeneity noted (Figure 3a–c). We found symptomatic improvement in 86% of patients treated with rifaximin compared with 40% of those treated with doxycycline and metronidazole (Figure 6).
Figure 5. (a–e) Results of comparative analysis: All 8 studies included in the comparative analysis are listed in all figures for reference. Excluded studies were removed from forest plots. CI, confidence interval; CP, chronic pancreatitis; GHBT, glucose hydrogen breath test; LHBT, lactulose hydrogen breath test; OR, odds ratio.
suggesting an alternative treatment strategy for patients with CP unresponsive to PERT.

The etiology of SIBO in CP is unclear. CP-associated intestinal dysmotility can lead to small bowel stasis (28–30), thereby increasing the likelihood of SIBO. The increased consumption of alcohol and narcotics in patients with CP was also suggested (18). In this review, 6 studies reported on alcoholic CP’s relationship to SIBO (16–18,21,23,31), and only Ní Chonchubhair et al. (17)

| Study                          | Year | Symptoms | Treatment                          | Clinical improvement after Rx                                                                 |
|--------------------------------|------|----------|------------------------------------|------------------------------------------------------------------------------------------------|
| Lee et al. (16)                | 2019 | Yes      | Not specified                      | Yes (pain, diarrhea, bloating, constipation, and weight loss)                                 |
| Ní Chonchubhair et al. (17)    | 2018 | Yes      | Rifaximin 400 mg t.i.d. for 10 d    | Yes (reduction in: flatulence, abdominal distension, abdominal pain, diarrhea, constipation, weight loss, fatigue, and body aches) |
| Kim et al. (24)                | 2016 | Yes      | Not reported                       | Not reported                                                                                   |
| Therrien et al. (18)           | 2015 | Yes      | Not reported                       | Not reported                                                                                   |
| Kumar et al (27)               | 2014 | Yes      | Rifaximin 400 mg t.i.d. for 14 d    | Yes (reduction in diarrhea)                                                                   |
| Signoretti et al. (31)         | 2014 | Yes      | Not reported                       | Not reported                                                                                   |
| Grigor’eva et al. (20)         | 2010 | Yes      | Not reported                       | Not reported                                                                                   |
| Mancilla et al. (21)           | 2008 | Yes      | Not reported                       | Not reported                                                                                   |
| Madsen et al. (25)             | 2003 | No       | Not reported                       | Not reported                                                                                   |
| Trespi and Ferrieri (23)       | 1999 | Yes      | Rifaximin 400 mg t.i.d. for 1 wk per mo for 3 mo | Yes (reduction in diarrhea and fecal fat)                                                      |
| Casellas et al. (22)           | 1998 | Yes      | Doxycycline 100 mg b.i.d. for 2 wk, then metronidazole 250 mg t.i.d. for 2 more wk | Yes (reduction in diarrhea)                                                                   |
| Bang Jørgensen et al. (26)     | 1991 | Not reported | Not reported                       | Not reported                                                                                   |
| Lembcke et al. (59)            | 1985 | Yes      | Not reported                       | Not reported                                                                                   |

Rx, treatment.

**Table 3. Treatment and response**

**Figure 6.** Response to treatment based on the type of antibiotic used. Treatment with rifaximin showed a higher response than doxycycline and metronidazole. Subgrouping by antibiotic regimen was able to eliminate heterogeneity in treatment response as evidenced by drop of $I^2$ from 38.3% to 0% in all subgroups. CI, confidence interval.
found it to have higher SIBO rates than nonalcohol CP. Narcotic use, investigated in 3 studies (16,17,27), showed no relation to SIBO prevalence (Figure S2C, see Supplementary Digital Content 1, http://links.lww.com/CTG/A93). In addition, the use of PPI is common in CP and might be a risk factor for SIBO, which was evaluated by 3 studies (16,17,31) in this review showing no significant relation to SIBO prevalence (Figure S2B, see Supplementary Digital Content 1, http://links.lww.com/CTG/A93). DM is associated with SIBO (32) and can affect up to 83% of patients with CP (33). We found it was associated with increased SIBO in CP (Figure 5a). Whether DM is reflective of pancreatic endocrine dysfunction leading to increased risk of SIBO is yet to be verified. Although the decline in pancreatic trypsin can disrupt the activation of defensin, hindering pancreatic antibiotic activity (34,35), the inhibition of pancreatic proteolytic enzymes does not impair this antibacterial activity (34). In addition, in canine models of PEI, PERT did not prevent intestinal microbial disruption (36). However, substituting cathelicidin-related antimicrobial peptide in mice deficient in acinar Orai1 protected them from fatal bacterial overgrowth (37). This suggests a direct effect of antimicrobials secreted by pancreatic acini and independent of digestive enzymes, which is consistent with recent findings by Frost et al. (3) showing exocrine pancreatic function to be a significant determinant of gut microbial load and diversity. In this review, we found PEI to be associated with increased SIBO in CP. We also found PEI to correlate well with SIBO prevalence, suggesting that antimicrobial pancreatic secretions might play a role in the pathogenesis of SIBO in CP. These results raise the question of whether direct endocrine/exocrine pancreatic gland destruction in CP is more important for SIBO development than external factors such as PPI, narcotics, or PERT.

All but one of the studies in this review used BTs to diagnose SIBO. LHBT showed significantly higher prevalence of SIBO in CP than GHBT (Figure 2c). This might be the result of accelerated intestinal transit delivering lactulose to colonic bacteria earlier than expected (18,38). Although GHBT is inherently more reliable as glucose is fully absorbed in the small intestine, glucose malabsorption rather than SIBO can result in positive GHBT (39–41). Despite attempts to standardize BT (42), they are still confounded by multiple technical issues, including the size of carbohydrate load, the osmotic and transit-accelerating effects of a highly concentrated substrate solution, test duration, and the adherence to dietary and other restrictions imposed by the test (42). Jejunal aspirate culture has long been the gold standard for SIBO diagnosis (43). It was used in one study (26) in our review. However, it also has its setbacks because of inaccessibility to the distal small bowel, potential for contamination, and false negatives for obligate anaerobes (44–46). In addition, when comparing culture to polymerase chain reaction analysis of jejunal aspirates, only 24.4% of jejunal bacteria are able to grow on standard media, raising questions about the ability of jejunal aspirate cultures to accurately reflect the intestinal bacterial load (41).

This degree of unreliability of current diagnostic techniques is reflected in the considerable heterogeneity among studies in this review. Accounting for differing results among diagnostic methods was able to explain 55% of the variance in SIBO prevalence in CP. Recent innovation using a swallowed capsule was able to measure in real time the concentrations of intraluminal gases such as H2, CO2, O2, and CH4. This technology provides much higher sensitivity than BT (47). Its clinical utility in SIBO diagnosis is yet to be verified. Therefore, although GHBT might provide practical and more reliable testing than LHBT, the diagnosis of SIBO in CP remains an elusive enterprise. Bacterial metabolomics and nucleic acid amplification techniques offer hope for more reliable testing in the near future.

CP is associated with malnutrition due to malabsorption of D-xylolose (48,49), glucose, folate (50), and neutral amino acids (51), as well as maldigestion due to PEI. Despite adequate doses of PERT, 43% of patients remain symptomatic (2). SIBO may result in malnutrition because of increased consumption of carbohydrates, proteins, and vitamins, as well as malabsorption of micronutrients resulting in lasting nutritional consequences (28,52,53). Signoretti et al. (31) reported on the association of SIBO in CP with nutritional status and found patients with CP complicated by SIBO to have significantly higher levels of folate, which is likely related to increased intestinal bacterial production of the compound (54). However, they had lower levels of vitamin D, although that only trended toward significance with a P value of 0.08. Lee et al. (16) found patients with SIBO in CP to have a significantly lower serum albumin level. They also found zinc deficiency, a known complication of CP (55,56), to be significantly more common in SIBO. Frost et al. (3) and Gubergrits et al. (28) found CP/PEI to alter intestinal bacterial composition, shifting the balance among species favoring some over others. These findings suggest that selective bacterial proliferation could be more important than mere numbers (8) when considering SIBO manifestations in CP. In addition, Ni Chonchubhair et al. (17) found patients with SIBO and CP to have more weight loss than their SIBO-negative counterparts. These results suggest SIBO might play a considerable role in malnourished CP patients.

Five studies in this review assessed response to SIBO treatment (Table 3). Our analysis showed a better response to rifaximin than doxycycline and metronidazole, suggesting rifaximin treatment might be of benefit to patients with CP unresponsive to PERT. Moreover, this response supports that SIBO is not merely associated with CP but also contributes to the clinical syndrome. Further studies to prove normalization of tests after antibiotic treatment would further support this role.

Celiac disease is associated with CP/PEI (57) and SIBO (13). In this review, only 2 studies (16,18) reported on celiac disease in their patient population. Whether this is a strong confounding factor potentially explaining the refractory symptoms and malabsorption seen in CP remains unknown. Lühr et al. (58) summarized PEI treatment guidelines to recommend testing for celiac disease after failure of PERT at double the recommended dose and adequate acid suppression to control symptoms. Although this subject has previously been presented in a systematic review by Capurso et al. (15), in this review, we provide the broadest and latest evidence on the prevalence, diagnosis, and treatment of SIBO in CP by including data from 4 additional studies and expanding on the analysis to factor in modifiers of SIBO prevalence in CP. Our rigorous analytic techniques using meta-regression were able to explain the heterogeneity among studies providing valuable insight into the possible role of PEI in SIBO in CP and diagnostic discrepancies. Moreover, we provide the first analysis in the literature into the outcomes of SIBO treatment in CP.

The limitations of our study include the retrospective nature of the included literature, which incurs associational data. Suboptimal design and quality of available evidence manifested in failure of most studies to address confounders such as concomitant
celiac disease and the unreliability of LHBT. We also noted heterogeneity in diagnostic testing and control group characteristics. These limitations have likely affected our conclusions; new research must take them into consideration.

In summary, under current diagnostic guidelines, SIBO complicates 38.6% (95% CI 25.5%–53.5%) of CP with an OR of 5.58 (95% CI 2.26%–13.75), indicating a predisposition for this condition. Although the etiology of SIBO in CP remains unknown, emerging evidence suggests a role for pancreatic exocrine dysfunction and DM as manifested by the association of PEI/DM with increased SIBO in CP. Discrepancies between diagnostic methods for SIBO are clear and pose a diagnostic dilemma. However, as the search and optimization of diagnostic testing continues, GHBT remains the test of choice. Our study shows antibiotic treatment of SIBO is associated with improved clinical outcomes (Table 3, Figure 6), suggesting an alternative strategy to treatment of patients with CP unresponsive to PERT.

**CONFLICTS OF INTEREST**

**Guarantor of the article:** Bara El Kurd, MD.  
**Specific author contributions:** Conception and design: B.E.K., M.M.L., and V.P.S. Screening of the literature: all authors. Data analysis: B.E.K., S.B., M.E.I., A.B., and V.P.S. Writing the manuscript: B.E.K. and V.P.S. Critical review of the manuscript: all authors.

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