Pancreatic enzyme supplementation

Agents which reduce gastric acidity in cystic fibrosis

Code: 032 **Updated:** December 5, 2025

Background

In CF inadequate buffering from bicarbonate-poor pancreatic secretions as a part of the effect in the CFTR protein defect may predispose to increased gastric acidity, contributing to a lower duodenal pH and leading to inactivate pancreatic enzymes replacement in case of pancreatic insufficiency, which in turn may induce increased gastric acidity. Heartburn, epigastric pain and gastric or duodenal ulcers may result from increased gastric acidity.

Exocrine pancreatic insufficiency associated to fat malabsorption in patients with CF is classically treated with pancreatic enzyme replacement therapy (PERT). Despite PERT, intestinal fat absorption remains insufficient in several patients with CF. A significant delay in the small intestinal transit and a deficient buffering capacity required to neutralize gastric acid in the proximal small bowel of patients with CF may have impact on timely release of PERT (Gelfond D et al, 2013). Based on this background it has been indicated that acid suppressive drugs could be helpful in individual CF patients to optimize fat absorption and/or nutritional status.

In the past data from registry and epidemiological reports reported that gastroesophageal reflux (GER) was common in patients with CF, with a prevalence ranging from 35 to 81%. Despite more than 50% of U.S. patients with CF were being treated with proton pump inhibitors it is not still clear whether GER may lead to more severe lung disease, including lower pulmonary function and increased numbers of respiratory exacerbations. Data regarding safety and efficacy of acid and non-acid agents in CF are lacking.

A recent review (Omecene NE et al, 2024) summarizes the evidence concerning the long-term use of PPIs and provides clinicians with guidance on how to approach deprescribing in their practice, suggesting to monitor CF-specific outcomes such as nutritional and respiratory status for a new therapy plan.

Issues

To assess the effect of major agents that reduce gastric acidity, such as proton pump inhibitors, including omeprazole and H2 receptor antagonists as ranitidine, cimetidine and famotidine, as well as further drugs such as prostaglandin E2 analogues and sodium bicarbonate, on:

1. reducing symptoms related to increased gastric acidity such as epigastric pain, heartburn;
2. improving nutritional status as assessed by weight, height and other indices of growth;
3. reducing complications of increased gastric acidity such as gastric or duodenal ulcers;
4. improving fat absorption, fecal nitrogen excretion and other measures of fat malabsorption;
5. improving lung function, quality of life and survival;
6. improving any adverse effects

What is known

One CDSR (Ng Sze May, 2016) evaluated 17 RCTs enrolling 273 patients with CF on 39 examined trials (22 failed to be suitable for inclusion).Proton pump inhibitors and H2 receptor antagonists were assessed compared to placebo or other treatments for evaluating the effects on fat absorption in addition to different doses of pancreatic enzymes. All the trials were carried out as single-centre (14 cross-over trials) and the duration of treatment was variable, ranging from five days to six months. Seven trials reported significant improvement in measures of fat malabsorption. Two trials reported no significant improvement in nutritional status. One trial found that drugs reducing gastric acidity improved gastro-intestinal symptoms such as abdominal pain. Only one trial reported also data on the potential efficacy of antiacid-agents on respiratory function. One trial reported adverse effect with prostaglandin E_2 analogue misoprostol. No trials were identified to assess the effectiveness of these agents in improving quality of life, complications of increased gastric acidity, or survival.

The same CDSR was updated in 2021 (Ng Sze May, 2021): trials showed limited evidence that agents that reduce gastric acidity are associated with improvement in gastro?intestinal symptoms and fat absorption. There was insufficient evidence to indicate whether there is an improvement in nutritional status, lung function, quality of life, or survival. Furthermore, due to the unclear risks of bias in the included trials, the Authors were unable to make firm conclusions based on the evidence reported therein, therefore they recommended to perform large, multicentre, randomised controlled clinical trials

A randomized controlled study in 17 adults with CF (DiMango E et al, 2014) showed a trend to earlier exacerbation and more frequent exacerbations in subjects randomized to assume esomeprazole (40mg twice daily for 36 weeks) compared with placebo. More recently (Ayoub F et al, 2017) it has been shown that exposure to proton pump inhibitors (PPI) is independently associated with a higher number of hospitalizations for pulmonary exacerbations in a cohort of CF adult patients. These data have been confirmed across a retrospective study (McCrory Be et al, 2018) that enrolled 126 patients in the PPI group (34.9% had an indication for both gastroesophageal reflux and enzyme enhancement) compared to 49 patients in the control group.

Data analyzed in the prospective Baby Observational and Nutrition Study, including 231 infants with CF and collecting several clinical

data over the first year of life, showed that *Pseudomonas* was recovered from at least one respiratory culture in 24% of infants and was associated with the presence of crackles/wheezes and use of proton pump inhibitors (PPI) (OR=5.47; 95% CI=1.36, 21.92; p=0.02) or PPI plus histamine-2 (H2) blocker (OR=8.2; 95% CI= 2.41, 27.93; p=0.001), but not in H2 blocker alone (Goetz D et al, 2019).

In a multicentre, randomized, double-blind, placebo-controlled trial children aged 4-18 years underwent 24-hour multichannel intraluminal pH-impedance monitoring. 22 consecutive patients with diagnosed GERD (median age 11.02± 3,67, range 6.4-17.0) were enrolled and assigned to omeprazole (20 mg twice daily) or placebo. A statistically significant reduction in abdominal pain and typical GERD symptoms, but not cough, was observed in both omeprazole (N=12) and placebo (N=10) groups. No statistically significant differences were observed between the groups in the degree of reduction. No adverse reactions were registered. Treatment of GERD in children with CF seems not to have a stronger effect than a placebo on the severity of cough and abdominal pain (Dziekiewicz M et al, 2021).

Recently (Shakir S et al, 2022) in a longitudinal cohort study of 32 patients (23 men; median age 32.5 years) with advanced CF lung disease (median FEV_1 24.8% predicted) starting elexacaftor-tezacaftor-ivacaftor, the reflux symptom index score and the sinunasal score significantly decreased at 6 months on treatment. Mean FEV_1% predicted rose by 9.2 points suggesting that addition to improving lung function and weight, CFTR modulators may improve upper airway and gastro-oesophageal reflux symptoms in advanced CF.

In a cohort study including paediatric and pwCF 80 patients matched with 80 nontreated patients based on sex, year of birth, CFTR genotype and pancreatic insufficiency received PPI for ?3 months. Over a median follow-up of 2 years, no significant differences in changes in BMI z-score were detected between groups. At baseline 25% (n = 20) of the treated patients and 22.5% (n = 18) of the untreated patients had a positive culture for PA that increased to 47.5% (n = 38) suggesting that **p**rolonged PPI therapy should be used cautiously in pwCF since it may increase the risk of respiratory infection by PA and does not seem to improve nutritional status (Zazzeron L et al, 2023).

19 patients aged 12 and older with CF and EPI were randomized in a pilot randomized, double-blind, placebo-controlled crossover trial (Philips AE et al, 2024) in order to evaluate whether proton-pump inhibitors (PPI) as an adjunct to pancreatic enzyme replacement therapy (PERT) may improve dietary fat absorption. Fat malabsorption via stool coefficient of fat absorption (CFA) and malabsorption blood test (MBT), gastrointestinal pH (wireless motility capsule [WMC]), and quality of life (QOL) were assessed after 14 days on both placebo or PPI (omeprazole). Main results reported 1 increased, 1 decreased, and 1 was within the reference range in both tests for fat absorption in the 3 subject results for CFA. For 9 MBT subjects, 7 decreased and 2 increased fat absorption. For the 4 WMC studies, no change in transit times, nor in pH profiles were noted. No differences were seen in the domains of the two QOL questionnaires comparing placebo and PPI. These limimed results did not suggest improvement in fat absorption attributable to PPI.

A longitudinal multicenter observational study (Liu C et al, 2024) was performed in order to evaluate the effects of acic blocker therapy (ABT) on growth, gut microbiome (GM), and early-onset lung disease in young children with CF in 145 infants with CF born during 2012-2017, diagnosed through newborn screening by age 3 months and followed to 36 months of age. Main results showed that ABT before age 3 years was frequent, with 81 (56%) of patients on H2 receptor antagonist (H2RA) or proton pump inhibitor (PPI), and higher among pancreatic insufficient (60%) versus pancreatic sufficient (26%) children. H2RA was commonly prescribed in infancy before transitioning to PPI. Growth improvements were not significantly greater, while GM ?-diversity at 3 years of age was significantly lower and early-onset lung disease more severe, in persistent ABT users compared to nonusers of ABT. These data suggested that early and persistent ABT use was not associated with significant growth benefits and instead showed associations with reduced GM diversity and negative effects on early-onset lung disease.

Unresolved questions

Adequately-powered, multicentered randomized controlled trials should be carried out in CF over a longer duration to provide further information of long-term effects on lung function and quality of life, as well as for comparing the efficacy of different agents for reducing gastric acidity.

Currently, there is insufficient evidence to indicate whether there is an improvement in nutritional status, lung function, quality of life or survival when antiacids are used.

The effect of new CFTR protein modulators on gastro-intestinal symptoms and GERD is in progress. As reported in a standardized withdrawal study in the era of HEMT decreases in dosing GI medication and PERT are already taking place without evidence to support this practice (Sathe M et al, 2023).

Keywords

Nutrition Disorders; Antacids;