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# Pancreatic Enzyme Replacement Therapy for Enterally Fed Patients With Cystic Fibrosis

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## Abstract

Administration of pancreatic enzymes (pancrelipase) to adult patients with cystic fibrosis when receiving enteral nutrition through a feeding tube is challenging. A number of techniques for preparing and administering the drug may result in complications that include feeding tube occlusion and inadequate enzyme delivery to the patient. A series of inpatient encounters is described. (*Nutr Clin Pract*. 2013;28:485-489)

## Keywords

enteral nutrition; food-drug interactions; pancreas; cystic fibrosis; enzymes

Patients with cystic fibrosis (CF) often require pancreatic enzymes (pancrelipase) to aid in the digestion and absorption of nutrients because they have varying degrees of exocrine pancreatic insufficiency. These exogenous enzyme products contain various amounts of lipase, protease, and amylase, which help to improve macronutrient absorption and reduce gastrointestinal (GI) complaints.[1-3] Approximately 11% of patients with CF may require enteral nutrition (EN) to supplement their oral intake.[4] Some patients with pancreatic insufficiency may be unable to consume pancrelipase orally because EN may be their sole source of nutrition for a period. This poses a significant challenge given limitations noted by the manufacturers in their product information.[5-10] In the absence of strong evidence-based recommendations, several techniques have been described for pancreatic enzyme replacement therapy (PERT) using the enteral feeding tube (EFT) in such patients.[11] The technique is important to the success of PERT. Administering pancrelipase capsule contents through an EFT should be performed in such a way as to ensure drug delivery to the GI lumen to allow adequate mixing with feeds. In general, consequences of inappropriate drug preparation and administration can include clogged tubes as well as altered drug response.[12]

Our institution manages a large group of adult patients with CF through an interdisciplinary practice. Members of the Clinical Nutrition Support Services participate in the care of these patients through an outpatient clinic as well as during any hospitalizations. These patients are at risk for a number of complications as a result of their primary disease, so the management of acute events should refrain from further increasing risk. Among potential complications are those that might arise from providing PERT to the enterally fed patient. Although our institution has specific protocols in place for administering medication by EFT, there were no guidelines specific for pancreatic enzyme administration at the time of these case reports. This article presents our recent experiences with PERT by describing several adult patients with CF who encountered varying degrees of success with EFT administration.

## Case Presentations

### *Case 1*

AD is a 35-year-old woman with a history of CF, type 1 diabetes mellitus, chronic pain, and nephrolithiasis admitted to our medical intensive care unit (ICU) with CF exacerbation. Her care included continuous EN (a low-electrolyte formula, 1.8 kcal/mL) administered at 40–45 mL/h over 24 hours via gastrostomy tube (GT). Free water flushes were provided as 200 mL every 6 hours. Her modest dose of pancrelipase (24,000 lipase units, Creon; AbbVie, Inc, Chicago, IL) was administered every 3 hours also through the GT. Instructions for administering the enzymes varied each time it was ordered. In the first 3 days of enzyme administration, with no specific instructions, the patient's feeding tube became obstructed, requiring ClogZapper (Corpak MedSystems, Buffalo Grove, IL) on 2 occasions. When subsequent orders were accompanied by instructions to "open capsule and dump contents into GT," the

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feeding tube again became obstructed, requiring ClogZapper every other day. Finally, the recommendation and ensuing order was made to "open and dissolve capsule contents in bicarbonate for 10–15 minutes" before administering via GT; this was further modified to specify the volume of 8.4% sodium bicarbonate injection to be dispensed. There were no subsequent obstructions of the feeding tube reported, and the patient was transferred to our long-term acute care (LTAC) unit and went on to receive an oral diet. During the entire admission, the enteral feedings were interrupted only for tracheostomy placement, routine flushing, drug administration, "declogging," and for 2 days during which the patient experienced high residual volume the "color of rust" related to a GI bleed.

The patient received the following additional medication through the EFT during this admission: acetaminophen liquid, bethanechol tablet, docusate liquid, fluconazole tablet, gabapentin capsule, senna liquid, potassium chloride liquid, lansoprazole disintegrating tablet, lorazepam tablet, magnesium oxide tablet, multivitamin without minerals, oxycodone tablet and liquid, PEG-3350, quetiapine tablet, and ranitidine liquid.

## *Case 2*

CW, a 27-year-old man with a history of severe CF with pancreatic insufficiency, type 1 diabetes mellitus, anemia, and right upper lobectomy, was admitted from an outside hospital for lung transplant evaluation. A GT was placed a week after admission, and EN (a concentrated formula) for weight gain was initiated at a rate of 100 mL/h for 12 hours. He tolerated the EN and the PERT throughout the admission. The patient received pancrelipase 60,000 lipase units (Zenpep; Zenpen, Aptalis Pharma US, Inc, Birmingham, AL) 3 times daily and as needed for snacks. During subsequent admissions for pulmonary infections/pulmonary exacerbations and listing for transplantation, he received EN (peptide-based formula) administered continuously at 65–95 mL/h over 24 hours along with the same dosing regimen of pancrelipase. No incidence of clogging occurred when orders specifically required the dilution of capsule contents with sodium bicarbonate injection before administration through the GT.

Several months after the initial admission and following an aborted attempt at lung transplantation, the patient was admitted to our LTAC unit. Although the patient continued EN (peptide-based formula) over 20 hours each day, pancrelipase was not ordered until day 7. During this period, the patient's feeds were held often due to significant GI discomfort despite rate reductions. When pancrelipase was restarted at 80,000 lipase units every 6 hours with orders to mix with sodium bicarbonate injection, the regimen provided incomplete relief of symptoms. Consideration (over a weekend) that the enzymes were causing some feeding intolerance led to dose reduction. Furthermore, orders were changed to mix the enzymes with applesauce prior to administration through the GT. This resulted in tube occlusion and possibly dislodgement during aggressive attempts at clearing the clog. The poorly functioning feeding tube required further evaluation and resulted in catheter placement with orders for parenteral nutrition (PN) for the next 4 days.

The patient received the following additional enteral medication during his LTAC admission: iron gluconate, lactulose, levofloxacin, magnesium oxide, metoclopramide, ondansetron, oxycodone, prednisone, PEG-3350, and a multivitamin.

## *Case 3*

RS is a 30-year-old man with a history significant for severe CF (requiring oxygen 6 L/h), pancreatic insufficiency, bowel obstruction, and ileostomy. He presented for bilateral lung transplantation on this initial admission with a GT already in place. Although initially started on PN due to hemodynamic instability, EN (a peptide-based formula) was administered as bolus feeds starting on hospital day 8. A routine bowel regimen was ordered before initiating the tube feeds, but no pancreatic enzymes were ordered at the time EN started. On hospital day 10, the patient experienced GI discomfort thought to be related to delayed gastric emptying. He was tolerating the EN so poorly that a gastrojejunostomy tube (GJT) was recommended. Pancreatic enzymes were still not ordered. The patient first received pancrelipase (24,000 lipase units; Creon) on hospital day 11, which was titrated to 2 capsules (48,000 lipase units) every 4 hours. The GT became clogged on hospital day 14 as a result of the pancreatic enzyme granules being administered directly into the feeding tube (ie, without any preparation). To better address the patient's needs, the EN regimen was modified to 140–240 mL (a low-electrolyte formula) every 4 hours. The enzyme order preparation was modified to dissolve a 325-mg tablet of sodium bicarbonate (containing 3.8 mEq bicarbonate) with the pancrelipase in water to be administered with each feeding. The patient tolerated this regimen without feeding tube obstruction. The primary team was concerned that the bicarbonate was causing the patient to become alkalemic (serum $CO_2$, 32 mEq/L) and discontinued the entire enzyme order. The team then used apple juice to dilute the enzymes, which was temporally related to subsequent complaints of abdominal cramping and loose watery stool output. Nutrition support team recommendations to once again dilute pancrelipase in sodium bicarbonate injection were followed. The patient's recovery was uneventful as he was eventually discharged on an oral diet and oral pancrelipase, with nocturnal EN.

The patient received the following additional enteral medication during this admission: amiodarone, aspirin, bisacodyl suppository, cotrimoxazole, docusate liquid, lactulose, lansoprazole, oxycodone, PEG-3350, quetiapine, senna liquid, sodium polystyrene sulfonate, tacrolimus, and voriconazole.

On an intervening admission to an outside hospital, an evaluation for obstruction was conducted following nausea and vomiting associated with his oral diet but not his nocturnal EN,

which he tolerated. His feeds were subsequently held and his access was converted to a GJT. The patient was discharged home on an oral diet along with supplemental nocturnal EN (low-electrolyte formula).

Six months following his initial admission, the patient presented following a cardiac arrest (pulseless electrical activity). The jejunostomy portion of the patient's GJT was clogged in the face of abdominal distension and diarrhea. The obstruction required use of ClogZapper twice before it cleared. Pancrelipase was finally ordered (120,000–144,000 lipase units; Creon) 3 times daily for oral, not enteral, administration ("do not give through the tube") for the next 5 days. Thereafter, the enzyme orders did not include a route of administration (dose of 48,000 lipase units every 6 hours). Sodium bicarbonate tablets were ordered to be mixed with the enzymes initially and later with sodium bicarbonate injection administered via a J-tube based on a nutrition support team recommendation. Within a week, EN was put on hold due to feeding tube obstruction requiring the use of ClogZapper again. The EN was changed to a peptide-based formula, and enzymes were discontinued due to suspected alkalosis (although serum $CO_2$, 23 mEq/L). At this time, the patient was noted to have high (1400 mL) stool output. He was negative for *Clostridium difficile* toxin, and a fecal fat study was normal. He required ClogZapper multiple times in the next few days and eventually underwent replacement of his jejunostomy tube by interventional radiology. The patient had more than 1 L of stool output while receiving EN (a peptide-based formula), so pancrelipase was again ordered (48,000 lipase units; Creon) every 6 hours with directions to mix with sodium bicarbonate injection. He continued to have loose stool output and was screened for *C. difficile* toxin again, which remained negative.

Additional medication on this admission included acetaminophen liquid, azithromycin, calcium carbonate, cholecalciferol, citric acid/sodium citrate, cotrimoxazole liquid, docusate liquid, lansoprazole, levetiracetam, magnesium oxide, phenytoin liquid, potassium chloride liquid, prednisone, senna liquid, tacrolimus, and voriconazole.

### *Case 4*

BS is a 22-year-old woman with a history of CF with pancreatic insufficiency who was admitted for a lobectomy and remained in the ICU postoperatively. She received pancrelipase (4000 lipase units, Pancreaze; Nordmark Arzneimittel GmbH & Co. KG, Uetersen, Germany) 4–5 times daily by mouth with meals for the first 4 postoperative days. The patient was reintubated the following day and then received EN (initially with a peptide-based formula) for two 8-hour infusions daily through an orogastric tube (OGT) (16 Fr). Pancrelipase was increased (16,000 lipase units, Pancreaze, 4 times daily), and the goal regimen of 70 mL/h was tolerated by the second day. For the duration of enteral feeding (changed to a low-electrolyte formula at 50 mL/h to better meet her needs), the patient's pancrelipase was ordered to be dissolved in 20 mL of 8.4% sodium bicarbonate, drawn up in an oral syringe, and administered through the OGT at the beginning of each 8-hour feeding. No problems were reported with this method of administration, and the patient did not experience signs or symptoms associated with malabsorption. On hospital day 20, the patient received a tracheotomy, and a percutaneous endoscopic gastrostomy tube was placed (18 Fr). The same pancrelipase dose (16,000 lipase units) was now administered 6 times daily. At this point, she began to complain of abdominal pain and was experiencing significant loose stool output (*C difficile* toxin negative), so the EN formula was changed (a peptide-based formula) without resolution. After reviewing the record, this was attributed to the enzymes being given sporadically. Subsequent pancrelipase was administered dissolved in sodium bicarbonate every 6 hours. The patient continued to report some abdominal pain and distension while in the ICU until being transferred to another facility 10 days later.

Additional medication on this admission included calcium acetate, cefepime (intravenous), bisacodyl suppository, docusate (liquid), furosemide, loperamide (liquid), PEG-3350, voriconazole liquid, and vitamins A, D, E, and K with zinc.

## Discussion

Prescribers and pharmacists share the responsibility with nurses for appropriate drug preparation and administration techniques. When present, a clogged tube serves as an indicator of poor access care (including an inadequate flushing regimen) and inappropriate medication preparation and administration. The obstruction of an EFT or altered drug effect should be a rare occurrence if best enteral practices are followed.[13,14] Tube obstructions are best prevented because effective methods for resolving clogs are not well studied.[15] Unfortunately, errors in drug preparation and administration can occur in about 60% of orders, based on a prospective observational study.[16] For pancreatic enzymes, the Food and Drug Administration–approved product labeling does not include recommendations for administering enzymes through an EFT and specifically prohibits crushing or chewing these enteric-coated products.[5-10] Crushing of a tablet or capsule contents that contain enteric coating is not recommended.[12,13] The immediate-release or powdered pancrelipase products are no longer on the market.

Several methods have been proposed for the administration of pancreatic enzymes in tube-fed patients, although none stands out above the others as an ideal technique. Successful administration of pancrelipase depends on a number of factors, including the available products and the enteral access device. To mimic oral administration, the capsule contents would need to be administered intact via a feeding tube with the distal end in the stomach. Administration of capsule contents—granules or microspheres—requires larger-bore feeding tubes (ie, at least 16 Fr) and still necessitates diluting the capsule contents

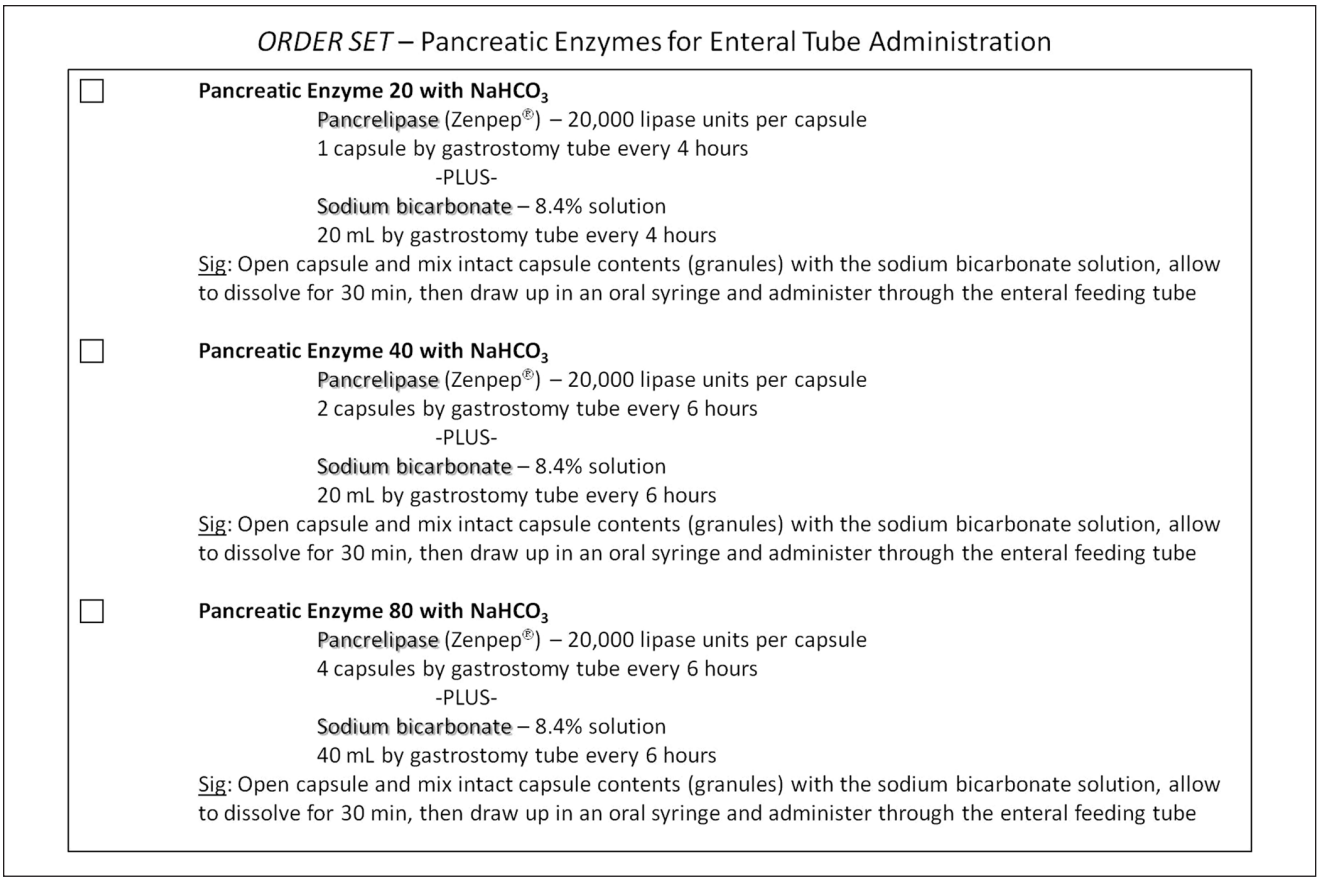


**Figure 1.** Order set for pancrelipase administration via an enteral feeding tube. Zenpep; Zenpen, Aptalis Pharma US, Inc., Birmingham, AL.

in a diluent solution for EFT administration. Water is usually the simplest and least problematic fluid for drug dilution prior to administration. Unfortunately, enteric-coated medications, whether crushed tablets or intact granules, are susceptible to increased adhesiveness when combined with water.[13] In the first and second cases presented above, dilution of pancrelipase in water prior to administration resulted in tube clogging. The heavily enteric-coated beads that make up the content of the Creon capsule are likely to stick together when wet and would be expected to pose a significant risk to tube patency.[17] An alternative is to suspend the granules in a thickened water-based fluid, but this creates the problem of further preparing the product and then the increased viscosity may pose additional problems, especially through smaller feeding tubes.

Using other liquids (eg, juices or carbonated beverages) considered acidic to preserve the enteric coating through the administration process is just as likely to cause clogging since the particles remain intact and sticky. These fluids are not recommended for use through an EFT in favor of water.[13] In the third case, dilution with hypertonic apple juice was associated with significant GI complaints as would be expected given not only the high osmolality but also the fructose and sorbitol content.[18]

Dissolving the enteric coating would require liquid of a higher pH. This is done at the risk of activating the enzymes and therefore needs to be cautiously administered in a timely manner to mix well in the lumen with the feeds. The best available recommendation may be to dissolve the uncrushed pancrelipase in a sodium bicarbonate solution, allowing it enough time to dissolve.[11] In our cases, when pancrelipase was diluted in sodium bicarbonate solution, there were no reports of EFT clogging. Our last case experienced no clogging problems at all as the pancrelipase was consistently diluted in sodium bicarbonate solution prior to administration. Given the reduced pancreatic secretion of bicarbonate in patients with CF, the volume of sodium bicarbonate administered is not expected to be a concern for the patients.

Avoiding pancrelipase administration is not an effective option. The third patient exhibited poor GI tolerance to EN without pancrelipase, even when receiving a peptide-based formula. When adherence to the enzyme regimen is relaxed, as in the fourth case, GI complaints increase.

Addition of PERT to the enteral feeding formula could be considered only in an open feeding system. However, pancrelipase should not be added directly to the feeds because the granules may begin to clump together and, if otherwise

activated, will begin to digest the feeds in the container, increasing the risk for tube obstruction.

Although the prescribing information prohibits mixing pancrelipase with the EN formula,[5,6,10] it does include sprinkling capsule contents on soft foods for patients unable to swallow the intact capsule.[5-8,10] To comply with the product prescribing information, attempts have been made to administer through a feeding tube after mixing pancrelipase capsule contents with soft foods. A specific product diluted in a distinct food may be feasible as long as the feeding tube is of sufficient diameter and short length.[19] The patient in the second case exhibited no problems except when the enzymes were mixed in with applesauce and when pancrelipase dosing was insufficient.

There is the possibility that other medications the patients received could have contributed to the tube obstructions. A review against available data suggests that these would be unlikely.[20,21] Given the diameter of the patient's EFT, it is unlikely that these medications, administered according to our longstanding protocol, would have contributed to tube obstruction. Although it is unclear whether the liquid medications were diluted adequately in all cases as appropriate for administration through the feeding tube, these may have contributed to abdominal and GI symptoms in the patient described in case 3. Otherwise, it seems most probable that inappropriate preparation and administration of the pancreatic enzymes were most likely responsible for EFT obstruction and GI complaints.

## Conclusions

With the exception of diluting pancrelipase capsule contents in sodium bicarbonate solution prior to administration, all other techniques used in our patients resulted in tube occlusion and/or continued GI complaints. We have since implemented a specific order set (Figure 1) for pancrelipase administration through an EFT without any complications noted. Our Pharmacy & Therapeutics Committee approved a protocol developed by an interdisciplinary group through our institution's Nutrition Committee. Using our electronic order entry system, prescribers use an order set titled "Pancreatic Enzymes for Enteral Feeding Tube Administration." The set includes several available frequencies and doses of pancrelipase to choose from and is then linked to an additional order for a volume of 8.4% sodium bicarbonate solution. The pharmacy then dispenses the labeled doses of pancrelipase capsules intact as a set along with the ordered volume of sodium bicarbonate solution. The patient's nurse mixes the capsule contents with the sodium bicarbonate in a closed, labeled, container in the medication room, allowing time to dissolve before drawing up into an oral syringe and administered via the EFT. Further research is needed to better describe all the clinical outcomes in these patients.

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