

PANCREATITIS

What's the Problem, and How Do You Diagnose It?

The pancreas is the gland located in the upper abdomen that secretes digestive enzymes into the small intestine and insulin into the bloodstream. Pancreatitis is a very serious inflammation of the pancreas which can sometimes be fatal. A significant percentage of people living with HIV may at some point experience this painful complication, most often when the pancreas becomes inflamed in response to a problematic drug. Extremely high triglycerides are another risk factor for development of pancreatitis. Genetic tendencies toward chronic pancreatic problems may increase the likelihood of developing this problem. Symptoms to watch for include upper abdominal or back pain, nausea, and vomiting.

Pancreatitis is generally diagnosed with blood tests. Amylase, a digestive enzyme produced in the pancreas and elsewhere, will normally be elevated with pancreatitis. The normal range for serum amylase is 60 to 160 Somogyi units/deciliter. With extreme pancreatic damage, amylase levels may actually be too low, indicating such extensive damage that little amylase is being produced. Increases in lipase, the fat-digesting enzyme, are another indication of pancreatitis, and this test is usually done along with the test for amylase. The normal range for lipase is 14 to 280 mIU/ml.

An ultrasound may also be performed. An enlarged pancreas with a distinct border may indicate pancreatitis.

What are the Causes?

Pancreatitis in HIV+ people most commonly results from the use of the nucleoside analogue antiretroviral drugs (nukes). It is thought likely that this occurs due to the damage to the mitochondria in pancreas cells that is caused by these drugs. In addition, the high level of oxidative stress that exists in HIV disease, combined with the worsening of the oxidative stress due to the mitochondrial damage, may greatly contribute to the creation of pancreatitis.

Of the nukes, ddI (Videx®) appears to confer the highest risk for pancreatitis. Other nucleoside analogues (AZT, 3TC, ddC, d4T, may also cause pancreatitis, although much less often. Certain combinations appear to greatly increase the risk for pancreatitis, including ddI with d4T (Zerit®) and/or hydroxyurea (Hydrea). In a warning letter to physicians issued by Bristol-Myers Squibb, it is stated that ddI, d4T, and hydroxyurea should be suspended in those with suspected pancreatitis; that reinstatement of d4T and/or hydroxyurea after a diagnosis of confirmed pancreatitis should be undertaken with caution; and that ddI should be permanently discontinued in patients with confirmed pancreatitis. The ddI package insert warns that individuals with risk factors for pancreatitis should use the drug with extreme caution and only if clearly indicated.

Some of the known risk factors for pancreatitis include (1) history of pancreatitis (2) ongoing alcohol abuse (3) morbid (disease-causing) obesity (4) hypertriglyceridemia (increased blood fats) (5) cholelithiasis (gall stones) (6) endoscopic retrograde cholangiopancreatography (dye test of bile ducts and pancreas gland) (7) other medications known to cause pancreatitis; and (8) medications known or thought to increase exposure to ddI (for example, hydroxyurea/Hydrea or tenofovir/Viread®). Of these, the sky-high triglycerides caused most often by protease inhibitors may be the most common additional risk factor in HIV+ people. It is thought that drinking any level of alcohol while taking ddI, ddC, or d4T, with or without hydroxyurea, can increase the risk of pancreatitis.

What are the possible treatments?

The first must for resolution of pancreatitis is immediate discontinuation of any drugs involved in its causation. As discussed above, ddI, d4T, and hydroxyurea should be suspended immediately in anyone with suspected pancreatitis. Beyond that, the standard medical treatment is sadly lacking in effective therapies. It consists of simply putting you in the hospital, giving you intravenous fluids, stopping all oral intake, treating the pain, and watching to see if you survive. However, research now supports the idea that mitochondrial dysfunction caused by antiretrovirals underlies pancreatitis, so addressing that problem should help.

Interestingly, one of the main ways in which the mitochondria can be supported is via the use of antioxidants. Well before the theories about mitochondrial dysfunction as a cause of pancreatitis surfaced, a number of studies had established that with both acute and chronic pancreatitis there is an increase in free radicals, those lethal little molecules that are already present in high amounts and causing so much damage in HIV+ people. Researchers who have studied this believe that the free radicals are involved in the development of pancreatic tissue damage. German researchers have reported significant success in reducing the mortality rate from pancreatitis with the use of antioxidant therapies to counter the free radicals.

Key Therapies

Antioxidant therapy. There are a number of studies that support the use of antioxidants, delivered either in intravenous solutions or orally, for the treatment of pancreatitis. In one study of 330 people diagnosed with acute pancreatitis utilizing CAT scans, selenium in the water-soluble form of sodium selenite was very effectively used. Immediately after the

diagnosis, 200 mcg of selenium was given intravenously in a bolus, followed by 800 mcg delivered over the next 24 hours. After this first day, a daily dose of 500 mcg of selenium was given. Compared to the previous norm, the mortality rate, the rate of complications, and the need for surgery decreased dramatically. Only 8 of the 330 patients died. The researchers note that complications occurred when the selenium dosing was delayed.

In another study of 99 patients with acute pancreatitis from different causes treated over a seven-month period, using selenium in doses from 200 mcg to 1,000 mcg daily along with 1,600 IU of vitamin E daily was found to be dramatically effective for reducing mortality, dropping the rate of death to 1.1 percent, compared to a previous average of 34 percent. This was an effective therapy regardless of the cause of the pancreatitis (alcohol-induced, idiopathic, post-traumatic, post-operative, etc.).

In another smaller study by the same researchers, none of the eight people with acute necrotizing pancreatitis who were given 500 mcg of sodium selenite (a liquid form of selenium) died, while 89 percent of those in the control group did. The researchers found that serum calcium levels normalized within 24 hours of beginning the therapy, while levels of oxidative stress markers decreased. Other studies have also shown less mortality, faster recovery, less pain, and shorter hospital stays in people suffering from pancreatitis who were given various forms of antioxidant therapy, including not only selenium and vitamin E but also vitamin C and N-acetyl-cysteine to raise glutathione. There have also been fewer relapses in those given antioxidants. Researchers have pointed out that the antioxidant therapy should be started as early as possible since the free radicals are generated early in the process of pancreatitis development.

We would note that the even better strategy is to use appropriate supplementation of a broad spectrum of antioxidants throughout the entire course of HIV disease, thus maintaining optimal levels of these important nutrients in the body at all times. There are many potential benefits from this. A decreased incidence of pancreatitis and lessened severity when it does occur may be among them. Adding to the antioxidants the B vitamins and carnitine that are also protective against mitochondrial damage would also be important. The best approach is definitely to combine all these nutrients, rather than just choosing one. Please refer to *the Mitochondrial Support and Protection Against Oxidative Stress* section of the *Introduction*, for NYBC's recommended protocol.

Glycyrrhizin. A licorice root extract known as glycyrrhizin, which comes in both capsule and sterile IV liquid forms, the IV form has been shown in clinical use in Japan to reverse pancreatitis, as well as having activity against hepatitis B, CMV and HIV. Japanese researchers also report that glycyrrhizin works as a potent anti-inflammatory and antioxidant, both of which would help counter pancreatitis. Using either the IV form or the oral form in combination with other antioxidants may prove helpful.

Magnesium. Researchers have established that people with acute pancreatitis who have low blood levels of calcium frequently have magnesium deficiency, even though their blood levels of magnesium will appear normal. These researchers suggest that the magnesium deficiency may contribute to the creation of the lowered blood calcium. It is well known that with magnesium deficiency, in general, the body will be unable to restore calcium levels until magnesium is normalized. Supplementation with magnesium (250 to 300 mg, twice daily) and calcium (500 mg, twice daily) would certainly seem an appropriate accompaniment to the antioxidant therapies.

Nutritional support. Researchers at the New York University Medical Center have pointed out strongly that appropriate nutritional support is extremely important with pancreatitis since failure to reverse malnutrition in those with acute pancreatitis may increase the risk of death. They suggest that parenteral (intravenous) nutrition should be used initially, with formulas that include fat emulsions in amounts sufficient to prevent essential fatty acid deficiency. When eating can be resumed, they stress that the diet should be low in fat.

Glutamine. Replenishing glutamine is also very important in the treatment of pancreatitis. Research has shown that a leaky gut, in other words, the damaged kind of intestines that so many people living with HIV have, may contribute greatly to the development of systemic infection and multiple organ system failure in people with pancreatitis. It appears that endotoxins escape from the gut, enter the circulation, and contribute to the organ failure. Dutch researcher Diep D. Tran, M.D., has suggested that future strategies should focus on the restoration of the gut barrier function, along with reducing the number of harmful gram-negative bacteria in the gut (so that they can't escape and cause the systemic infection). Both human and animal studies have shown that L-glutamine can help to restore the barrier function of the intestine (the way it blocks the uptake of bacteria and other pathogens, improperly digested food, and so on).

Ketotifen also appears to be **protective of the cells in the gastrointestinal tract**, protecting cells in the stomach, small intestine, and colon from toxins. In non-HIV research, it has shown some effectiveness as a treatment for colitis, or inflammatory bowel disease. *Thus, it may also provide some protection against the damage to the intestines commonly*

caused by inflammation and pathogen-produced toxins. This could help preserve gut function and, thus, proper absorption of nutrients, making a nutrient program more likely to succeed. Ketotifen is available without a prescription through NYBC.

Rather than waiting for the crisis of a pancreatitis episode, the far better approach is to use glutamine or Ketotifen consistently throughout this disease process for all the benefits that can give, including maintaining the health of the intestines, including not only the barrier function but also absorption of nutrients. Glutamine also maintains muscle tissue, providing fuel for immune cells, and maintaining immune protection in the linings of the body via appropriate production of secretory IgA. However, if you haven't done this, it is crucial for glutamine to be included in any intravenous nutrition that is given.

According to Douglas Wilmore, MD, Professor of Surgery, Harvard University, and an internationally renowned and widely published researcher on this amino acid, glutamine should be added to a TPN solution at a dose of 20 grams of l-glutamine per liter of solution, a concentration which approaches its maximum solubility. Because glutamine is not a standard addition to TPN formulas and the dipeptide which is highly soluble isn't available in the U.S. as yet, this must be done in a pharmacy with the proper facilities to prepare the TPN solution. Alternatively, the solution can be manufactured by a home care company that makes TPN (for example, Coram Healthcare) and the solution can be brought into the hospital. Dr. Wilmore says that the usual person with a moderate illness needs about 30 grams of glutamine per day which is compatible with 1.5 or so liters of TPN per day. He also notes that additional glutamine would not be harmful as long as there is reasonably good renal and hepatic function.

Since a number of people have reported difficulties in obtaining glutamine to add to their IV solutions, note that TPN solutions containing glutamine are available through Coram Healthcare, a large company that provides home infusion therapies, and other alternate site healthcare services. There are 88 Coram locations across North America, including in most U.S. states as well as in Ontario, Canada. Although only a few of their facilities can make up the TPN solution, there is no need to have a facility near you. The only requirement is for a physician to call in a prescription for the TPN formula; it can then be prepared at one of the main facilities, and shipped via Fed Ex for next-day delivery. The contact info for Coram is as follows: Coram Healthcare's main toll-free number for information is 800-423-1411. Coram Healthcare's main website is: <http://www.coramhc.com> At this website, choose Branch Locations to locate the list of Coram facilities.

Dietary changes. When the person with pancreatitis has recovered sufficiently to again begin eating, it will be very important to choose foods that will be the least stressful to the pancreas. Avoiding fried foods, or any other high-fat, difficult-to-digest foods is crucial. It is best to stay away from fast foods and other highly processed foods. Instead focus on fruits, vegetables, and rice or other non-gluten containing grains (millet, quinoa, buckwheat). Foods such as the dark-skinned berries (blueberries, boysenberries, dark cherries, blackberries) and the dark yellow or orange fruits and veggies (butternut squash, pumpkin, and carrots) are relatively easy to digest and can be soothing sources of a potent amount of antioxidants and natural anti-inflammatories.

Pancreatic enzymes. When eating food is resumed, it will be very important to take pancreatic enzymes with all meals and snacks. This will reduce the demand on the pancreas to produce these, and help ensure proper digestion when the pancreas is still not functioning properly. It will usually be helpful to take 2 to 6 tablets with each meal. If pain is felt in the next few hours after eating, it may also help to take an additional 1 to 2 tablets at that time. NYBC's **Plant Ultra Enzymes** are an excellent digestive enzyme, since they are from vegetable sources and is active in a wide pH range.