

CHRONIC PANCREATITIS: WORKING ON THE MISTAKES

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*We learn from our mistakes,
from others' — make a career.*

M. Zhvanetskiy

We really intend to learn from our mistakes, but far from being able to make a career out of other others'. On the contrary, we would like to summarize both our and others' mistakes. Results of this work on the mistakes would improve the diagnostics and treatment of chronic pancreatitis (CP).

For many years, the pancreas has remained mysterious misunderstood organ for doctors of various specialties: internists, gastroenterologists, surgeons, oncologists, geneticists, doctors of instrumental diagnostics, laboratory doctors. In patients' turn, diagnose of pancreatic disease is associated with prolonged and often uninformative diagnostic procedures with ineffective, expensive treatment.

Despite numerous studies, the diseases of the pancreas are usually difficult to diagnose and hard to treat. Up to date, the mortality from acute pancreatitis has remained high, diagnosis of CP in the early stages is a test for the physician, its treatment has disappointing results, the therapy of cystic fibrosis is reduced to symptomatic with poor outcome, and cancer of the pancreas is a fatal disease. Diagnosis and treatment of "little giants" of the pancreas are not very successful — neuroendocrine tumors are generally small in size, but with diverse severe manifestations. This state of pancreatology has been stated for more than 100 years, and even modern pancreatologists still consider the pancreas "*mysterious stranger*" [10, 11, 25].

Although new laboratory and instrumental methods of diagnostics, modern ways of treating diseases of the pancreas have been developed in recent years, the practical yield is poor.

Diagnostics of diseases of the pancreas is rather complicated. That's why such diseases are usually diagnosed late. Hence it appears the high frequency of disability, complications, mortality. For example, the frequency of diagnostic errors in CP reaches 45% [7]. Let's examine the reasons for this situation:

- non-specificity and diversity of clinical manifestations;
- close topographical and functional relations of the pancreas with other bodies (in relation to the pancreas, adjacent organs should be considered not only the stomach, duodenum, transverse colon, especially its splenic angle, but the left kidney, spleen), which defines the complexity of interpretation of clinical symptoms, and a high frequency of comorbidities;
- great compensatory potential of the pancreas contributes to the fact that its long-lasting functional tests show normal values; this is the reason for late diagnostics of pancreatic insufficiency;
- polyetiology of pancreatitis and a variety of pathogenetic mechanisms leading to their development, often do not allow even a set of diagnostic tests "to hit the mark," more than 20% of the cases are being considered as idiopathic CP;
- frequent development of pancreatitis as secondary diseases — outcome, consequence of other diseases, mostly of the digestive organs; patient is still being treated as before, if the doctor did not pay attention to changes in the nature, timing of pain, etc., and hence did not conduct "pancreatic" tests;
- retroperitoneal location of the pancreas makes it difficult to conduct the imaging and morphological study.

All these provisions are fundamental, and they are difficult to change.

How do we fix these errors, or at least try to fix it?

First of all, we must remember the mandatory three consecutive components of the diagnostics of CP. The first of them is to make sure that the patient really suffers from CP. Let's refer to the modern M-ANNHEIM classification [24].

According to this classification, there are three forms of CP.

Definite CP is diagnosed by the presence of one or more of the following additional criteria:

1. calcification of the pancreas;
2. moderate or evident changes of the ducts;
3. severe exocrine insufficiency (steatorrhea, which clearly yields to the therapy by enzyme preparations);
4. typical histological picture of CP.

Possible CP is defined by the presence of one or more of the following additional criteria:

1. minimal changes of ducts;
2. recurrent or constant current pseudocyst;
3. pathological results of functional tests of exocrine pancreatic function (e.g., fecal elastase test);
4. endocrine pancreatic insufficiency.

Borderline CP is already diagnosed CP with typical clinical picture, but without the criteria of probable or definite CP.

Another special etiological variant of CP is specified.

Alcohol — in addition to the above-mentioned criteria of definite, probable or borderline CP, at least one of the following factors is present:

1. excessive alcohol consumption in history (men >80 g/day for several years, women — smaller dose);
2. increasing alcohol consumption in history (20-80 g/day for several years);
3. moderate alcohol consumption in history (<20 g/day for several years).

Unfortunately, these criteria for the diagnosis of CP in practice are rarely taken into account, which leads to overdiagnosis. At the second stage of diagnostics we must identify risk factors, causes, complications and outcomes of the disease. All this

will have fundamental importance in the future for the development of tactics of treatment (Table. 1).

Table 1

**Recommendations for elimination (treatment) of risk factors
and etiologic factors of pancreatic pain in CP**

(according to S. S. Olesen et al., 2013 [21])

Risks/etiological factors	Treatment	Comments
Smoking	Quitting smoking	Reduction of disease progression, reduction in pain intensity
Food	Specific recommendations are absent	No evidence
Heredity	Monitoring the state of the ducts in the dynamics Pancreatectomy	No evidence With the high risk of malignancy
Pancreas divisum	Endoscopic or surgical treatment	Results are contradictory
Autoimmune CP	Glucocorticosteroids	Treatment results are convincing
Metabolic disorders	Lipid-lowering therapy, treatment of hyperparathyroidism and others.	Necessary to consult an endocrinologist
Peptic ulcer	Proton pump inhibitor +/- Helicobacter pylori eradication	Exclude NSAIDs
Pseudocyst	Endoscopic, percutaneous drainage, surgical treatment	The method of treatment depends on the location, size of the pseudocyst, histology
Obstruction of the duodenum	Endoscopic dilation or surgical treatment	Endoscopic dilation — the treatment of first choice
Obstruction of the common bile duct	Stenting	Data on the relationship of the bile duct obstruction with pain contradictory

Only when there is no apparent reason of CP upon careful diagnostic search, you should diagnose of idiopathic pancreatitis, which provides for only pathogenetic and symptomatic treatment (Fig. 1).

At the third stage of diagnostics it is necessary to identify comorbidities of digestive organs (often) or other internal organs (rarely), which may provoke aggravation and exacerbate CP course (biliary pathology, gastroduodenal erosive and ulcerative lesions, bacterial overgrowth syndrome in the small intestine, abdominal ischemic syndrome, etc.) [3].

To avoid diagnostic errors, careful clinical diagnostics and the right choice of laboratory and instrumental methods are extremely crucial. Upon CP in the absence of pathognomonic symptoms and, conversely, the presence of comorbidities and a range of possible etiological factors, it is very important to conduct thorough direct study of the patient, have sufficient clinical experience and depart from the modern stereotype of "the doctor-manager" who only appoints additional research. I cannot but recall in this regard the statement of my great-uncle academician M. M. Gubergrits: "You need to take off your hat before Mr. Roentgen, but not your head".

Let's turn to diagnostic errors in regard to the selection and interpretation of results of additional research methods and start with the activity of pancreatic enzymes in the blood (urine). Every practitioner knows that there are cases of absence of increasing α -amylase and other enzymes of the pancreas in blood (urine), even upon expressed CP aggravation. How can this be explained? The fact is that in acute pancreatitis initially healthy pancreatic tissue is damaged, when acini contain large amounts of enzymes. Upon cytolysis of acinar cells, these enzymes go into the blood. In this regard, rates of pancreatic enzymes in blood (urine) are always clearly increased in acute pancreatitis. Upon CP cytolysis of acinar cells occurs in a situation when the pancreas parenchyma is fibrosed, atrophic in one or another way. Therefore, before the beginning of CP exacerbation production of enzymes is usually decreased. During exacerbation increase occurs, but from the initially reduced level. It turns out that rates usually do not exceed the upper limit of the generally accepted norms. It is necessary to remember that there are exceptions in acute pancreatitis. In particular, in severe necrotizing pancreatitis high hyperenzymemia may not develop.

We consider it important to pay attention of practitioners to the following facts. Many enzymes of the pancreas are not pancreatospecific (α -amylase, lipase, etc.), so

pancreatospecific enzymes could be more informative (pancreatic isoamylase, trypsin). You should keep in mind that upon pancreatic insufficiency activity of these enzymes in biological fluids may even decline. And yet — declines in α -amylase cannot even be found, as the deficiency of pancreatic isoamylase is "overlapped" by the normal production of salivary isoamylase (α -amylase is a sum of pancreatic and salivary isoamylase). If we are talking about hyperenzymemia, then the true hyperenzymemia should be considered as increased more than 3 times indices. Less evident increase in indicators of enzymes of the pancreas can occur upon out-pancreatic pathology (disease of the salivary glands, intestine, lungs, chronic renal failure, etc.).

In the literature we can find a lot of studies that show rapid positive dynamics of fecal elastase-1 under the influence of a particular treatment. It seems unrealistic. Reduction of fecal elastase test results reflects the presence of fibrosis and atrophy of the parenchyma of the pancreas with the deterioration of its functional state. It is hard to imagine the rapid elimination of any kind of treatment of these processes. Fecal elastase-1 is very inert index. In the clinic of internal medicine n. a. Prof. A. Y. Gubergrits of Donetsk National Medical University we assign fecal elastase test for CP patients not more than 1 time in 3 years. Of course, this is a reflection of our subjective experience as research evidence on this issue has not been performed. In addition, by assessing the dynamics of the test results, we only control the speed of progression of CP and pancreatic insufficiency, but this dynamics does not have any significant impact on the treatment. Fecal elastase test worldwide is considered as screening test for the detection of exocrine pancreatic insufficiency. It is known that elastase-1 is a pancreatospecific enzyme that is almost not destroyed during passage through the digestive tract. This test has a favorable cost/information value ratio. In addition, it is almost non-invasive and affordable. We believe that this test should be routine in clinical practice. Of course, it has drawbacks too, e.g., low information content upon mild pancreatic insufficiency. But its information value, in any case, is much higher than the informativeness of scatoscopy. Adherence to the scatological study in the CIS countries is a typical manifestation of "delay syndrome", i.e. the

conservatism of doctors. We must honestly admit a lack of awareness of physicians regarding modern methods of diagnostics in pancreatology and their opinion about the high cost of fecal elastase test. To judge from the experience of our clinic, "the game worth the candle", i.e. promptly detected exocrine pancreatic insufficiency and consequently promptly appointed enzyme replacement therapy have a much greater importance in maintaining a satisfactory quality of patients' life, preserving their working ability than the ephemeral "one-off" value of spending a big amount of money.

We mentioned above that the dynamic control of the degree of reduction of indicators of fecal elastase-1 is not critical. The fact is that, upon the detection of pancreatic insufficiency, the proper dose of "gold standard" of enzyme therapy Creon should be prescribed. This dose is equal to 40000-50000 FIP lipase units for the main meal and 10000-20000 FIP lipase units for lunch [19, 25].

More informative for the diagnostics of pancreatic insufficiency are breath tests, especially triglyceride breath test. But it is more expensive and not available everywhere. If possible, of course, these tests should be preferred.

Let us turn to the interpretation of instrumental methods. The most frequently prescribed is sonography. We want to emphasize that it is available, but only a screening method. According to different authors, the sensitivity of conventional ultrasound in CP is 37-94% and specificity is 48-82%. It is important that the conclusion "diffuse changes of the pancreas" without identifying calcifications, pseudocysts, expansion Wirsung's duct is not an sufficient basis for the diagnosis of CP. Some of the patients with such diffuse changes and typical clinical picture of CP really suffer from early stages of the disease, but they need verification of more accurate methods (computed tomography, magnetic resonance imaging, magnetic resonance cholangiopancreatography) [3].

Conventional sonography reveals the following CP features: enlarged pancreas, changes of its shape, contour, echogenicity, structure, duct system, compression or deformation of the vessels, adjacent organs, the presence of cystic formations. Identification and interpretation of these symptoms is difficult because of the

retroperitoneal location of the pancreas, bloating, excess subcutaneous fat and parapancreatic fiber, nonspecific ultrasound picture. Particularly, tail of the pancreas is poorly visualized. Additional difficulties arise in children when the left lobe of the liver covers the acoustic window, complicating the location of the head of the pancreas. In assessing the contours of the pancreas, it must be considered that in the initial stage of CP and even acute pancreatitis contours of the pancreas remain sharp and smooth. At the same time, in 10-20% of healthy people, the contours of pancreas are unsharp and uneven. Evident changes in organ contours depend on the degree of development of parapancreatic fiber. Upon mild and moderate fiber, contours are clearly defined, and upon the excess one — less clearly [14].

Not always we should expect enlarged pancreas in CP because of its infiltration and edema. Often, these processes occur on a background of atrophy and sclerosis of the parenchyma, that is why the pancreas is not only enlarged, but sometimes (rarely) even diminished. We should take into account the age of patients. Size of the pancreas in young people is bigger than in the elderly as its atrophy comes with age. Size of the pancreas depends on the scanning plane. In some cases even prolonged constipation helps to increase the size of the tail of the pancreas without changing its echostructure, enlargement of the pancreas during the ultrasound after the elimination of constipation can't be determined [14].

Especially pronounced subjectivity of ultrasound diagnostics of CP is in the evaluation of echogenicity of the pancreas. We should consider the age and the degree of nutrition of the patient. Echogenicity in the young people is lower than in the elderly, i.e. increased echogenicity of the pancreas in an elderly patient should not be considered as a sign of CP, if there are no other symptoms. Conversely, normal echogenicity of the pancreas does not preclude the initial stage of CP. Excessive development of parapancreatic fiber and fat infiltration of the pancreas also increase its echogenicity in sonography. Heterogeneity of structure is also non-specific [14].

In our experience, sonography is not enough for the diagnostics of CP. Certainly, it is necessary to take into account the clinical picture. We often use multislice computed tomography from the instrumental methods. Our view is

consistent with the opinion of other authors [3]. Endoscopic sonography should be more widely applied in practice, which is currently the most informative method in pancreatology [14].

Physicians should be aware that in difficult diagnostic cases, in patients with autoimmune pancreatitis — necessarily, pancreatic biopsy under control of the endoscopic sonography should be carried out. Usually it is a needle biopsy, but it also has higher information value than the routine laboratory and instrumental methods.

It is clear that correct treatment can be prescribed only upon proper and timely diagnostics of CP, functional pancreatic insufficiency, identifying causes and complications of the disease.

Treatment of pancreatitis is a difficult task for physicians, surgeons, gastroenterologists. This is due to the versatility of the pathogenesis of inflammation of the pancreas, with a lack of knowledge about its etiology and pathogenesis, with the frequent presence of not only local but also systemic manifestations, complications of the disease. Unsatisfactory results of treatment are also associated with late diagnostics of pancreatitis. In addition, the "mysterious stranger" passes through its parenchyma very few drugs (special difficulties arise because of this when it comes to selecting antibacterial drugs; only a few tenths of a percentage of constant dose of protease inhibitors penetrate into the parenchyma of the pancreas).

In practice, not only etiotropic, pathogenetic, but even the symptomatic treatment of pancreatitis is ineffective. One of the severest manifestations (pain syndrome) can be driven by a variety of mechanisms. Pathogenesis of functional insufficiency of the pancreas, its diagnostics and choice of enzyme preparation are also complicated, so not all the patients compensate the decline of exocrine function of the organ.

Particular attention should be paid to the possibility of etiotropic treatment. In this regard, particular success can be achieved upon biliary pancreatitis in some patients with gallstone disease after cholecystectomy in obstructive pancreatitis associated with papillostenosis, big duodenal papilla adenoma, after endoscopic or

surgical decompression. In some cases, the principal is the pathogenetic treatment, such as treatment of autoimmune pancreatitis with corticosteroids.

Treatment is usually directed at CP two main clinical syndromes: pancreatic insufficiency and abdominal pain. In the first case, early diagnostics and adequate doses of enzyme preparations are of fundamental importance, as discussed above. Physicians should be aware that you should not wait for steatorrhea, which reflects a preservation of not more than 10% of the functionality of the parenchyma of the pancreas, and the emaciation of the patient. Upon exocrine pancreatic insufficiency, the whole body of the patient suffers due to the shortage of energy, plastic material, vitamins, macro- and microelements. Manifestations of pancreatic insufficiency are very diverse and relate to all organs and tissues. And in this respect awareness of physicians suffers again, which deficit our Ukrainian Pancreatic Club is trying to make up for. Doses of Creon, smaller than the above-mentioned, do not lead to a sufficient level of digestion. Their prescription is palliative, and pancreatic insufficiency continues to progress.

In respect of relief of pain, doctors often make the mistake of assigning tableted enzyme preparations. This approach in the present conditions is beneath criticism.

In the late 70s of the last century, the mechanism of inhibition of pancreatic secretion is described by a feedback mechanism, and then it was confirmed that the intraluminal administration of trypsin or chymotrypsin inhibits the secretion of enzymes [13, 18, 22]. In the 80s, the use of tablets of non-covered enzyme preparations with high proteolytic activity to reduce pain in CP was justified [15].

Recommendations of the Russian Gastroenterological Association rightly and clearly state that such tableted enzyme preparations without acid-fast cover are not registered in Russia (and in other CIS countries), so they are inaccessible, and there is no evidence on the enteric coated tablets registered in the CIS [5]. The lack of registration non-covered enzyme preparations for the relief of pancreatic pain is marked in the recommendations for the treatment of CP in other countries, including the European ones [23]. Nevertheless, in the CIS countries papers continue to be

published in which the authors recommend to use the tableted non-covered enzyme preparation Mezym forte or tableted enteric coated enzyme preparations Mezym 10000 or 20000 for the relief of pain in CP [4, 8]. These recommendations, in our view, have no basis.

Meta-analysis (6 randomized trials — 186 patients) and Cochrane review (2 parallel and 8 cross-sectional studies — 361 patients) did not obtain reliable data on pain relief by non-covered enzyme preparations — they were effective in less than half of the patients [12, 20].

Despite the convincing results of modern high-evidential research (level 1 A), the adherents of series Mezym drugs continue to keep to outdated algorithm of American Gastroenterological Association for relief of pain in CP, which included non-covered tableted preparations [26]. Thus, the authors of the mythical and, fortunately, debunked idea without hesitation or not knowing (or maybe for some other reasons), extrapolate obtained 30 years ago, very modest and not without defects of design, data on the efficacy of tableted pancreatin on registered tableted preparations [2].

Various schemes with these drugs, such as three-phase one (step up or step down) [4], have no logical or evidentiary justification.

Due to the negative results of the meta-analysis and Cochrane review [12, 20], European recommendations on the treatment of CP specifically and clearly indicated that the enzyme preparations should not be used for the relief of pain [16, 17].

Some recommendations [23] exclude tableted non-covered enzyme preparations with a high content of proteases, registered only in the US from the main therapeutic action, but point out the possibility of their application *ex juvantibus* (the results of the meta-analysis show that there is a chance to get the effect in young women, upon non-alcoholic etiology of pancreatitis, with pain of type B, without or with mild exocrine insufficiency of the pancreas [12, 27]).

We have tried for many years to convince CIS doctors not to prescribe tableted enzyme preparations for the relief of pancreatic pain, arguing the above evidential data and our own experience. Let's give more convincing information about the drug

Viokase that is registered in the US and approved by the FDA. It is these drugs that were previously used for the relief of pain. Currently preparation Viokase is prescribed only for treatment exocrine pancreatic insufficiency in adult patients and only in combination with a proton pump inhibitor (to prevent enzyme inactivation in the acidic environment of the stomach) [www.Viokase.com]. At least 4 tablets of Viokase 16 or 8 tablets of Viokase 8 are prescribed for intake. For information: Viokase 8 contains 30000 USP protease Units, Viokase 16 — 60000 USP protease Units. This corresponds to 480 FIP and 960 FIP protease Units, i.e. 15.5 tablets of Mezym forte for one intake. In addition, the patient must take another proton pump inhibitor to preserve enzyme activity during passage through the stomach. So, to achieve the mythical result which is rejected by modern definitive studies, the patient should take a handful of pills.

Detailed treatment strategy of exocrine insufficiency of the pancreas and abdominal pain in CP is described in Recommendations of the Ukrainian Pancreatic Club, which are published in a separate annex to the third issue of the "Gerald of the Pancreatic Club", 2014 [1, 6].

Combining all the facts, we should definitely strive for progress in pancreatology and seek to create not just new tests and new treatment options, but true results. We need to break free from the burden of the mystery of the pancreas, to unveil "veil" of this stranger. While we did not succeed fully, we present the practical aspects of modern pancreatology, trying to equip doctors with recommendations and algorithms that they can actually use in their daily work on the diagnosis and treatment of CP.

We are sure to cope with the problem of diagnostics and treatment of this complex disease, and we can fix them after work on the mistakes.

Only that is a mistake

Which is not fixed.

Confucius

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The article presents a critical analysis of the most common mistakes made by general practitioners in the diagnostics and treatment of chronic pancreatitis. Ways of accounting and eliminating these mistakes are outlined.

Fig. 1. Algorithm of finding the cause of idiopathic pancreatitis [9]. Before proceeding to a survey by the algorithm, it is necessary to study carefully the complaints, history, conduct an objective examination, routine laboratory tests, X-ray studies of the chest, transabdominal sonography, computed tomography.

ИП — idiopathic pancreatitis, КТ — computed tomography, УДХК — ursodeoxycholic acid, ЭРХПГ — endoscopic retrograde cholangiopancreatography.

