

## PANCREAS AND ENZYMOLOGY IN PEDIATRICS

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**Key words:** pancreas, pancreatic enzymes, exocrine secretion, replacement therapy, children

Digestion is a single, integrated process because of the close linkages between different parts of the digestive tract. Impairment of the function of one of the gastrointestinal tract, usually leads to frustration in other organs. In different parts of the digestive tract occur various processes of absorption of nutrients. Important organ of the digestive system in the body is the pancreas.

It is known that the pancreas is located in the retroperitoneal space, is the formation of length 14–18 cm and a weight of about 85–100. Under physiological conditions, the pancreas forms a day from 50 to 2500 ml of secretion. Pancreas performs two important functions in the body — the endocrine (production of insulin and glucagon — the main hormones that regulate carbohydrate metabolism) and exocrine (formation and deposition of various enzymes that hydrolyze nutrients).

Enzymology history began in 1833, when A. Payen and J. Persaud established the role of diastase during fermentation of sugar into alcohol. Diastase got its name from the Greek word meaning "separation". For a long time diastase was called all enzymes (from Latin fermentum — fermenting yeast). German physiologist V. Kuehne in 1878 suggested the name "enzyme" (from the Greek words en zimon — "in leaven") not only for enzyme fermentation, but for all others, including enzymes and digestive system. As the detection of other catalysts of chemical processes in living systems at the suggestion of enzymes E. Duclos (1898) became known for hydrolyzable substrate by attaching the end -aza. At the end of the XIX — the beginning of the XX century, it was found that enzymes exert their activity not only in

living cells, but even after their destruction. Isolated, purified and crystallized enzymes from the pancreas of cattle began early last century.

In clinical practice, the enzymes of plant, fungal and bacterial origin (solizim, Oraza) have some advantages over enzymes derived from the pancreas of pigs and cattle (acid resistance and relative cheapness). However, their lipolytic and amylolytic activity ten times weaker, and proteolytic — no, that is responsible for their limited use.

Pancreatic insufficiency limits food intake and leads to disruption of processes of absorption. Enzyme replacement therapy is the main focus in the treatment of patients with the syndrome of impaired digestion.

### **Participation of the pancreas in digestion**

At receipt of food in the gastro-intestinal tract of the pancreas secretes into the small intestine the pancreatic enzymes and bicarbonates, neutralized with hydrochloric acid. List of key enzymes of pancreas and their involvement in digestion are shown in Table 1.

Table 1

### **Digestive pancreatic enzymes**

<b>Enzymes</b>	<b>Secretion form</b>	<b>Action</b>
$\alpha$ -amylase	Active	Cleavage of polysaccharides into maltose and maltotriose
lipase	Active	Hydrolysis of triglycerides to form fatty acids and monoglycerides
phospholipase A	The proenzyme is activated by trypsin	Hydrolysis of phosphatidylcholine to produce fatty acids lizofosfatilholin
Карбоксилэстераза	Active	Hydrolysis of cholesterol esters and esters of fat soluble vitamins
trypsin	The proenzyme is activated with enterokinase	Cleaves proteins and polypeptides within the protein molecule
chymotrypsin	The proenzyme is activated by trypsin	Protein cleaves internal connections in the area of aromatic amino acids, leucine, methionine, glutamine
elastase	Proelastase activated with trypsin	Cleaves elastin, a protein of

Carboxypeptidase A and B	Proenzyme activated by trypsin	connective tissue Cleaves a peptide bond to the carboxyl terminus of aromatic (A) and base (B) amino acid residues
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Basic hydrolytic processes occur in the small intestine where nutrients are broken down into monomers are absorbed and enter the blood and lymph. The processing of nutrients in the small intestine takes place in three successive interconnected stages:

- cavitary digestion;
- membrane digestion;
- absorption.

Enzymes hydrolyzing fats and carbohydrates ( $\alpha$ -amylase, lipase) are secreted in an active state, proteolytic enzymes (trypsin, chymotrypsin, elastase, carboxypeptidase) — as zymogens that are activated in the lumen of the small intestine. Intestinal enzyme places an important role in their activation — enterokinase, which transmits trypsinogen to active trypsin. Trypsin, in turn, activates the proteolytic enzymes remaining. During cavitary digestion carbohydrates (starch, glycogen) to split pancreatic amylase disaccharides and small amounts of glucose.

Under the action of proteolytic enzymes produced low molecular weight peptides and small amounts of glucose. Fats in the presence of bile pancreatic lipase to hydrolyze the di-and monoglycerides, fatty acids and glycerol. Lipase most rapidly loses its activity, and in the ileum normally determined only by an insignificant amount.

Proteases, particularly amylase, are more stable and retain, respectively 30 and 45% of its activity in the terminal small intestine. The basis of reduction of lipase activity is under the influence of its proteolysis and proteases, especially chymotrypsin. Uneven enzyme activity from the proximal to the distal small intestine observed in healthy individuals and, particularly, those with exocrine pancreatic

insufficiency. This explains the fact that develops much earlier violation fat digestion than starch or protein.

### **Causes of digestive disorders**

Exocrine pancreas dysfunction occurs in various diseases. Pancreatic dysfunction due to developing:

- ***maldigestion*** — maldigestion (splitting) of food polymers (proteins, fats, carbohydrates) to the suction necessary for the components (monoglycerides, fatty acids, amino acids, monosaccharides);
- ***malabsorption*** — malabsorption of nutrients, leading to an eating disorder patient expressed.

The main causes of indigestion, malabsorption and maldigestion accompanied by children are the following:

### **Insufficiency of cavitory digestion:**

- pancreatogenic internal secretorial insufficiency (chronic pancreatitis, pancreas stones, subtotal pancreatectomy, pancreas cancer, pancreas fistula, cystic fibrosis, malignant malnutrition);
- reduction in the activity of enterokinase and inactivation of pancreatic enzymes in the gut (Zollinger-Ellison syndrome, duodenal ulcer, duodenitis, intestinal dysbiosis);
- violation of the transit of intestinal contents and violation mixing enzymes with food chyme (duodeno-and gastrostasis, irritable bowel syndrome, post-vagotomy and drainage operations);
- reduction in the concentration of enzymes as a result of dilution (post gastrectomy syndrome, intestinal dysbiosis, a condition after cholecystectomy);
- violation of products cholecystikin, pancreozymin, secretin deficiency of bile acids in the small intestine, congenital or acquired (biliary obstruction,

severe hepatitis, primary biliary cirrhosis, the pathology of the terminal small intestine, small intestine dysbiosis, cholestyramine treatment);

- gastrogene failure (gastrectomy, gastrectomy, atrophic gastritis).

**Violation of membrane digestion** — congenital or acquired disaccharidase lactase or other failure, the intracellular transport of food components as a result of the death of enterocytes (Crohn's disease, gluten enteropathy, sarcoidosis, radiation, and other ischemic enteritis).

**Violation of the outflow of lymph from the intestine** — obstruction of lymphatic ducts (limphoangectaziya, lymphoma, tuberculosis, cancer, carcinoid).

**Combined disturbance** (diabetes, giardiasis, hyperthyroidism, hypogammaglobulinemia, amyloidosis, AIDS).

It is recalled that *in practice is more common secondary or relative, pancreatic insufficiency* is usually caused by taking an unusual food, its excess amount or inflammatory diseases of the upper digestive canal. The latter is associated with the development of secondary mechanisms relative exocrine pancreatic insufficiency.

Exocrine pancreatic insufficiency is based on the following mechanisms (Alexandr Yakovenko, 1998, with modifications):

- pancreatic immaturity;
- destruction of acinar cells (decreased synthesis of enzymes);
- obstruction of the pancreatic duct, pancreatic juice flow violating the duodenum;
- reduced secretion of bicarbonate ductal epithelium of pancreas, leading to acidification of the duodenal contents to pH 4.0 and lower, resulting in denaturation of pancreatic enzymes and bile acid precipitation;
- failure due to lack of activation of enzymes and bile enterokinase;
- dyskinesia duodenum and small intestine, so that there is a violation of mixing enzymes with food chyme;

- violation of intestinal microbiocenosis (inactivation of enzymes and destruction), hypoalbuminemia due to lack of protein in the diet (violation of enzyme synthesis).

### **Clinical signs of exocrine pancreatic insufficiency**

It is now well known clinical signs of severe pancreatic insufficiency. Appears badly digested bowel movement of fatty nature, often gray in color, with a sharp unpleasant odor. Patients complain of flatulence, often pain, flatulence, loose stools. Body weight is reduced, sometimes at a quite good appetite. Symptoms of vitamin deficiency due to reduced revenues fat-soluble vitamins (A, D, E, K).

With all the variety of diseases involving pancreatic insufficiency, the task of the physician is to spending a differential diagnosis, to establish the cause and correction in a timely manner. To clarify the diagnosis and detection of exocrine pancreatic insufficiency using different research methods.

### **Methods for objective assessment of exocrine pancreatic function**

The methods of objective assessment of exocrine pancreatic function include the following:

- direct method — analysis of the content (activity) of blood and urine amylase;
- coprogram;
- study the content of pancreatic enzymes in the duodenal secretions;
- quantification of fat in feces;
- determination of enzymes in the feces (elastase test);
- ultrasound of the pancreas;
- endoscopic retrograde cholangiopancreatography;
- CT and magnetic resonance cholangiopancreatography.

Laboratory methods include **determination of pancreatic enzymes in the blood and urine**. The level of amylase activity in blood and urine was increased 5-10 times in acute pancreatitis; level of lipase and amylase activity in blood at

exacerbation of chronic pancreatitis can be a normal or temporarily increased (up to 2 times). Provocation of hyperamylasemia by neostigmine, methylsulfate, pancreozymin, glucose constitutes a violation of the outflow or inflammation of the pancreas. Increased elastase-1 in plasma reflects the severity of inflammation in pancreatitis. The increased activity of trypsin in serum indicates an exacerbation pancreatitis with a progressive course of chronic pancreatitis reduced immunoreactive trypsin activity level and the ratio of "trypsin / insulin" refers to the phase of the disease.

Table 2 lists the diseases that may be accompanied by an increase in the level of activity of pancreatic enzymes.

Table 2

**Diseases that may be accompanied by an increase in the level of activity of pancreatic enzymes**

<b>Elevated levels of amylase activity</b>	
Pancreatitis during treatment with opiates	Intussusception of the small intestine
Carcinoma of the pancreas	Parotitis
Enterobrosia	Cholecystitis
Ileus	Cirrhosis
Myocardial intestinal wall	Hepatitis
Retrograde pancreatography	Chronic liver failure
<b>Elevated levels of lipase activity</b>	
Myocardial intestinal wall	Ileus
Retrograde pancreatography	during treatment with opiates
Intussusception of the small intestine	Carcinoma of the pancreas
Pancreatitis	Enterobrosia

**Scatological study** that allows to diagnose, monitor the development of the disease and treatment, evaluate the state of the digestive functions of the gastrointestinal tract should be carried out prior to the appointment of pancreatic enzymes. Advantageously to use 105 g protein, 135 g fat, and 180 g carbohydrates for

3 days of Schmidt. In the pathology of the pancreatic scatological study reveals the following pathologic features:

- *steatorrhea* — presence in the stool of neutral fat (steatorrhea type 1), fatty acid soaps (steatorrhea type 2) a combination of both (steatorrhea third type);
- *creatorrhoea* — a large number of muscle fibers (+ + or + + +), which is normally found in the feces is very little;
- *amylorrhoea* — plurality of starch grains in the feces showing inappropriate carbohydrate fermentation, which occurs in patients with pancreatic insufficiency.

The earliest sign of exocrine pancreatic insufficiency is steatorrhea; kreatoreya appears much later; amylorrhoea rarely observed.

**Study of the content of pancreatic enzymes** in the duodenal secretion (basal, with secretin stimulation [1 U / kg], 0.5% hydrochloric acid, pancreozymin [1 U / kg]) to determine the types of secretion:

- *hypersecretion type* observed at mild inflammatory degenerative changes of pancreas; it is characterized by a high concentration of enzymes at normal or elevated levels of volume and bicarbonate secretion;
- *hiposecretory type* characteristic of the pancreas fibrosis, with this type of observed normal or reduced volume of juice and bicarbonate levels with reduced enzyme activity;
- *obstructive type*, detectable with duct due to obstruction papillita, duodenitis, spasm of Oddi's sphincter, and in this case there is a reduced amount of juice with normal enzymes and bicarbonates.

**Quantitative determination of fat in feces.** Making testing daily intake of 100 grams of fat within 23 days is required on the eve of the study and 3 days of the test. The fat content in stool is estimated by (adding sudan to feces) the most informative method. It allows you to determine the overall total amount of fat in the feces, taking

into account exogenous fat (food) origin. Normally the feces segregates no more than 10% from fat, dietary administration. Increasing this number indicates disorders of digestion and absorption of fat.

**Determination of elastase-1 in feces.** Elastase-1 — proteolytic enzyme pancreas. Elastase-1 concentration in the stool reflects the degree of exocrine pancreatic insufficiency:

- normal activity of elastase-1 in stool in children older than 1 month, and adults is 200 mg / g of feces;
- elastase activity fluctuations in the stool-1 of from 100 to 200 mg / g of feces show a moderate degree of exocrine pancreatic insufficiency;
- declines in activity of elastase-1 in stool less than 100 mcg / g of feces reveals severe degree of pancreatic insufficiency.

However, published data on the use of this technique are contradictory. Thus, some authors argue that the determination of the activity of fecal elastase-1 more sensitive than other methods of diagnosis of chronic pancreatitis, but the results are not reliable in the case of lung disease course. Assessing the level of activity of fecal elastase-1 only helps in determining the severe deficiency of exocrine pancreatic function. Thus, the application of elastase test to determine or exclude exocrine pancreas failure (acute and chronic pancreatitis, cystic fibrosis, Shvahnman syndrome, isolated lipase deficiency), as well as to monitor the state of the exocrine function of the organ without canceling enzymotherapy.

**Ultrasound examination of the pancreas** reveals an increase in its size, change of echolucency (edema, induration), the presence of inclusions of echolucency; assess the state of Wirsung duct.

**Endoscopic retrograde of cholangiopancreatography** — using this technique is possible to identify expansion and deformation of the main pancreatic duct strictures and detection of calcium deposits on the walls of the ducts, pancreas parenchymal calcification. In the study also revealed changes in the biliary system:

stenosing papillitis, choledocholithiasis, developmental abnormalities of the bile ducts and gall bladder, and other.

**Computed tomography and magnetic resonance cholangiopancreatography** — the main indication for these studies in children are complicated course of acute and chronic pancreatitis, suspected surround process in the pancreas and adjacent organs.

### **Correction of exocrine pancreatic insufficiency**

Currently in clinical practice, a large number of enzyme preparations with different components and combinations of enzymatic activity (Table 3). Depending on the composition of enzyme preparations can be divided into several groups:

- extracts of the gastric mucosa, the main active ingredient of which is pepsin (abomin, atsidin-pepsin);
- pancreatic enzymes — amylase, lipase and trypsin (pangrol, pancreatin, mezym forte, creon);
- combined preparations containing pancreatin in conjunction with the components of bile, hemicellulose, and other additions (digestal, festal, panzinorm forte, enzistal);
- plant enzymes — papain, fungal amylase, lipase and other enzymes (pepfiz, yunienzim, solizim);
- combined enzyme preparations containing pancreatin in combination with plant enzymes, vitamins (wobenzym);
- disaccharidase (tilaktaza).

Table 3

### **Composition of enzyme preparations**

<b>Drug's name</b>	<b>Lipase FIP Units</b>	<b>Amylase FIP Units</b>	<b>Protease FIP Units</b>	<b>Other components</b>
Pancreatin	4300	3500	200	
Mezym forte	3500	4200	250	
Mezym forte 10000	10000	7500	1000	

Pangrol 10000	10000	9500	500	
Pangrol 25000	25000	22500	1250	
Festal H	6000	4500	300	Bile — 25 mg Hemicellulase — 50 mg
Creon 10000	10000	800	600	
Creon 25000	25 000	18 000	1000	
Panzinorm forte	6000	7500	2000	Cholic acid — 13,5 mg
Enzistal	6000	4500	300	Bile — 25 mg Hemicellulase — 50 mg

Note: FIP Units — international unit of enzyme activity.

The preparations obtained from the first group of the gastric mucosa pigs, calves or lambs, they contain proteolytic enzymes that contribute to the release of gastrin, which is a regulatory polypeptide. They are used in functional disorders of the gastrointestinal tract, gastritis with secretory insufficiency. These drugs should not be prescribed with exocrine pancreatic insufficiency.

The second group of drugs contributes to the digestion of proteins, fats and carbohydrates, they are appointed as replacement therapy for exocrine pancreatic insufficiency. These enzymes contribute to the relief of clinical signs of exocrine pancreatic insufficiency, which include loss of appetite, nausea, rumbling in the abdomen, bloating, steatorrhoea, creatorrhoea and amylopoiesis. Pancreatin preparations will not affect the function of the stomach, liver, biliary system and motility of the intestine, but can reduce the secretion of pancreatic.

Combination products containing pancreatin along with bile acids, hemicellulase, simethicone and other preparations containing bile acids, and pancreatic secretion increase cholepoiesis stimulate intestinal motility and gall bladder. Drugs prescribed for lack of exocrine pancreatic function in conjunction with the pathology of the liver, biliary system, in violation of the chewing function,

sedentary lifestyle, short-term gaps in food; hypoacid or patients with gastritis anatsidny. Hemicellulase, a part of some drugs (festal), promotes the breakdown of fiber in the lumen of the small intestine, normalization of intestinal microflora. Many enzyme preparations contain simethicone or dimethicone, reduce the degree of the surface tension of gas bubbles, thus they dissolve and are absorbed by the walls of the stomach or intestines, it helps to reduce flatulence. Enzyme preparations containing components of bile, contraindicated in patients with acute / chronic pancreatitis, acute / chronic hepatitis, diarrhea, gastric ulcer and duodenal ulcer, inflammatory bowel disease.

Enzyme herbal preparations contraindicated in patients with fungal and domestic sensitization, bronchial asthma. Enzymes from vegetable raw materials can be used for correction of exocrine pancreatic insufficiency, especially in cases where the patient can not tolerate the pancreatic enzymes (allergy to pork, beef). Nowadays enzymes of fungal origin and vegetable are not widely used in practice due to the low enzyme activity (75-fold less effective than preparations of animal origin).

**Recommendations on the choice of the enzyme preparation:**

- drugs should not reduce the pH of the stomach should be dissolved in the small intestine at pH 5.0 and above;
- drugs should not cause diarrhea, since high levels of bile acids in the intestine and increases the secretion of pancreatic intensive enzyme therapy can cause hologen diarrhea;
- it is necessary to provide a shell that protects enzymes from digesting gastric juice;
- enzymes should be rapidly released in the upper small intestine;
- preparations should be well tolerated, does not cause adverse reactions;
- enzymes should be of animal origin (are more resistant to the action of hydrochloric acid);

- preparations should be composed of lipase cleaving lipids and provides thermal balance of the body;
- preparations should have microspheroidal form (less than 2 mm in diameter), providing a large contact surface with the chyme.

Most enzyme preparations are in the form of tablets / pills diameter of 5 mm or more in enteric-coated to protect them from destruction by hydrochloric acid. These drugs are not practically used in children under three years of age due to the inability of the child to swallow a pill or pills entirely. Violation of the same acid-resistant membrane integrity of these drugs leads to a significant reduction in the effectiveness of therapy. Consumption of a dosage form having a diameter greater than 5 mm and helps delay the drug in the stomach, its leveling action.

Advantages of minigranulated microspherical shapes and pancreatic enzymes are that they are rapidly and homogeneously mixed with the chyme and transported into the duodenum, where at  $\text{pH} > 6.0$  for 30 minutes to 97% released enzymes. Microgranular form of drugs you can use them in children from an early age. Children under one year of microspheres capsule and pour out, count the numbers required and give a drink of water during a meal. It should be drunk after with a non-alkaline liquids. It is important to consider micro tablet does not remain in the mouth and is not chewed. Sufficiency dose clinical trial (normalization of stool frequency and nature) and laboratory parameters (disappearance of steatorrhea and creatorrhoea in coprogram normalization of triglycerides in the lipid profile of the chair).

Dose of enzyme preparation is selected individually during the first week of treatment, depending on the severity of exocrine pancreatic insufficiency. Dose appropriate to calculate the enzyme preparation by lipase (enzyme preparations have low lipase activity is Treytsa ligament and lipase play a key role in digestion). You should start with a small dose (1000 FIP Units of lipase per kg). In severe exocrine insufficiency using 4000-5000 FIP Units of lipase per kg per day. The drug should be taken with meals, 34 times a day. Course duration is determined individually.

At the absolute pancreatic insufficiency (cystic fibrosis, hereditary pancreatitis, congenital enzyme deficiency syndrome Shvahmana etc.) lifetime replacement therapy is high doses of enzymes microgranular. Children with reactive changes pancreas enzyme therapy is recommended to use "on demand" for the relief of the clinical manifestations of malabsorption, pain.

**Contraindications of digestive enzymes use:**

- acute pancreatitis in the first 710 days;
- exacerbation of chronic pancreatitis in the first 35 days;
- inflammatory bowel disease (Crohn's disease and ulcerative colitis);
- allergic reactions to bovine or porcine in medical history.

Precautions enzyme preparations used in patients with gout.

In case of failure of digestive enzymes **is necessary** to eliminate one of the possible reasons:

- inactivation of the enzymes in the duodenum resulting acidification of its contents;
- concomitant diseases of the small intestine (worm infestation, gut dysbiosis, etc.);
- duodenostasis;
- failure patients the recommended treatment regimen;
- the use of enzymes that lost their activity.

Side effects associated with the use of enzyme preparations are extremely rare (less than 1%). These include: abdominal discomfort, hyperuricemia, impaired absorption of folic acid (complex formation), fibrosis of the terminal part of the ileum, an allergic reaction to pork protein, irritation of the mucous membranes of the mouth, skin irritation perianal area, constipation (in overdose). Therapy enzyme preparations should be differentiated, taking into account the mechanism of the disease (Table 4).

**Choice of enzyme preparations for diseases of the gastrointestinal tract in children (by E. P. Yakovenko, 1998, with modifications)**

Pathology	Leading scatological sign	Enzymes preparations
Chronic pancreatitis	Steatorrhea type 1	Creon, pantsitrat
Chronic liver disease	Steatorrhea type 2; creatorrhoea rarely steatorrhea type 1	Creon pantsitrat, other drugs pancreatin
Erosive and ulcerative lesions of the gastrointestinal mucosa	Various changes	Creon pantsitrat, other drugs pancreatin
Chronic gastritis with secretory insufficiency	Creatorrhoea with striations, the presence of connective tissue	Panzinorm, digestin
Pathology of the biliary system, excluding miliary hypertension	Fatty acid soap	Preparations containing pancreatin and bile components (festal, digestal etc.)
Cholestatic liver disease	Fatty acid soap	Preparations based on pancreatin + + geptral or ursodeoxycholic acid
Functional disorders of the gastrointestinal tract caused by dysbiosis	Cellulose amyloorrhea, iodophilic flora	Preparations based on pancreatin + hemicellulase

Note: GIT — gastrointestinal tract. The presence of a doctor at the disposal of high-level and micro granular micro granulated drugs can significantly improve enzyme therapy

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## **Pancreas and enzymology in pediatrics**

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Article describes physiology of exocrine pancreatic function. Composition of pancreatic juice and phases of pancreatic secretion are described. Mechanisms underlying exocrine pancreatic insufficiency and the factors contributing to the development of this state in children are considered. Research methods of exocrine pancreatic function are presented. Guidelines for choosing the enzyme preparations are presented too.