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OPTIMIZING THE DIAGNOSIS AND TREATMENT IN CHILDREN WITH ACUTE PANCREATITIS

SUMMARY

The acute pancreatitis pathophysiology is so far poorly understood.
– The cholecystokinin is one of the factors causing acute pancreatitis, which leads to changes in cell's cytoskeleton and to exocytose blocking. A comprehensive clinical and instrumental examination in 100 patients with acute pancreatitis at the age of 3-18 years who were treated in the urban Children's Hospital, V. Ignatenko - Chisinau, Republic of Moldova was done.

Inclusion criteria were: the age of 3-18 years and the confirmed diagnosis of acute pancreatitis.

Exclusion criteria were: children under 3 years old and patients with acute pancreatitis of unknown etiology, children with severe concomitant diseases, patients who violate the physician's recommendations.

The 100 children were divided into the following Groups: Group I - control group, which included healthy children (20), Group II - patients with acute pancreatitis during the onset period (40); Group III - patients with acute pancreatitis who received standard treatment, and GUNA BOWEL low dose medicine (30); Group IV - children with acute pancreatitis who received standard treatment (30).

All patients were examined according to a special protocol at the onset of the disease and 1 month after the treatment.

GUNA BOWEL was included in the regimen from the onset period of acute pancreatitis in children in the dosage of:
- **Children under the age of 2 years, 3 drops 3 times per day.**
- **Children from 2 to 6 years, 5 drops 3 times per day.**
- **Children from 6 to 10 years, 10 drops 3 times per day.**

The inclusion of GUNA BOWEL contributed to the normalization of the necrotic concentration. In the children who received standard treatment the levels of necrotic substances remained elevated.

The level of middle molecules is 1.4 times higher, and necrotic substances are 1.6 times higher compared with the same parameters in healthy children.
The concentration of these substances reached the normal range in the patients who received GUNA BOWEL.

The introduction of GUNA BOWEL in the standard treatment for children with AP contributes to a more rapid stabilization of oxi-redox system enzymatic biochemical disturbances, NO and endogenous intoxication.

KEY WORDS **ACUTE PANCREATITIS, PEDIATRICS, OXI-REDOX SYSTEMS, GUNA BOWEL**

INTRODUCTION

The acute pancreatitis pathophysiology is so far poorly understood.
The pathophysiological processes in the pancreas occur at the level of **acinar cells**.

– Cholecystokinin is one of the factors causing acute pancreatitis, which leads to changes in cell's cytoskeleton and to exocytose blocking [3, 5].

This contributes to trypsinogen's transformation into trypsin, as well as the activation of other proteases [1, 2, 8, 10]. The proteolytic enzymes realize lipids' membrane peroxidation, creating favorable conditions for the oxidative stress and for the activation of cytosolic nuclear factor kV (NF-kV).

The main diagnostic indicators in the implementation of the pathogenesis of acute pancreatitis are the following: trypsin, chymotrypsin, elastase, Ca^{2+}, PAF (platelet activating factor), kallikrein, TNFα, interleukins (IL 1, 6, 8), and nitric oxide.

In spite of the considerable success in defining the pathogenesis of acute pancreatitis, some issues remain unresolved, including the role study of the disease progression biochemical mechanisms.

The antioxidant barrier is a complex set of enzymes, elements and substances that are formed for the defense of aerobic organisms, preventing the formation of free radicals.

In recent years, a special interest is paid to antioxidant therapy in the treatment of acute pancreatitis.

The main enzymes with antioxidant effect are SOD (superoxide dismutase) and glutathione peroxidase [4, 7, 9]. One of the biomarkers of oxidative stress is malondialdehyde (**MDA**) which appears in the body as a result of polyunsaturated fatty acids' degradation in the absence of antioxidants.
– SOD is the first line of defense in the oxidative stress [6].

The endogenous intoxication (**EI**) is a model system dynamically developing pathological process, inclined to progression.
EI is caused by a combination of several factors: the enhanced formation of tissue disintegration products with subsequent resorption; catabolism and accumulation in the body of a large amount of secondary metabolites; suppress the functional activity of the natural systems of detoxification.
EI contributes to difficult removal and delay of excreta tissue, the disturbance

of the elimination processes of the metabolism final products from the body, as a consequence of the accumulation of toxins and waste products of infectious agents [9, 10].

Lack of acute pancreatitis efficacy treatment requires the introduction of new methods of diagnosis and therapy.

OBJECTIVE OF THE STUDY

Identification and correction of endogenous intoxication and oxi-redox system indicators in **children with acute pancreatitis**.

MATERIAL AND METHODS

A comprehensive clinical and instrumental study in **100 patients** with acute pancreatitis (age 3-18 years) who were treated in the urban Children's Hospital V. Ignatenko Chisinau - Republic of Moldova was done.

– Inclusion criteria were: the age of 3-18 years and the confirmed diagnosis of acute pancreatitis.

– Exclusion criteria were: children under 3 years old and patients with acute pancreatitis of unknown etiology, the children with severe concomitant diseases, the patients who violate the physician's recommendations.

The 100 children were divided into the following Groups: **Group I** - control group, which included healthy children (**20**), **Group II** - patients with acute pancreatitis during the onset period (**40**); **Group III** - patients with acute pancreatitis who received standard treatment, and **GUNA BOWEL** low dose medicine (**30**); **Group IV** - children with acute pancreatitis who received standard treatment (**30**).

All patients were examined according to a special protocol at the onset of the disease, and 1 month after the treatment (follow up).

Patients were carried out clinical, biological, instrumental examination (ultrasound of the Digestive Apparatus and pancreas with postprandial load, endoscopy) and from the biological analysis blood and urine tests were performed, using biochemical and enzyme immunoassay methods defining serum amylase, ALT, AST, total bilirubin and its fractions, total proteins, urea, glucose, and cholesterol.

Lipid peroxidation products: HPL (early, transient, and late) and the hexane fraction isopodan, MDA, AOP (antioxidant protection, and the hexane isopodan fraction), nitric oxide were determined in the blood serum for the oxidative stress.
Indicators of endogenous intoxication (middle molecules, necrotic materials).

– The standard treatment of acute pancreatitis includes diet and 5 medications therapy:

- Proton pump inhibitors: omeprazole - 1mg/kg/day x 2 doses, or lorazepam 0,05–0,1 mg/kg/day;
- Enzymes therapy (pangrol, mezim 500-1000 IU of lipase on 1 kg body weight/dose) during the meal - 2 weeks;
- Antispasmodics: expressed pain syndrome [Duspatalin (mebeverine), Buscopan®] - 2-3 weeks;
- Antibiotics (cephalosporins, 2nd-3rd generation, aminopenicillin) in case of intoxication syndrome with fever, inflammatory changes in blood analysis in children with acute bronchitis and pneumonia;
- Intravenous perfusion: 5% glucose solution, 0.9% sodium chloride solution (detoxification and rehydration).

GUNA BOWEL (Guna Laboratories, Mian - Italy) has a detoxication action and stimulates intestinal motility.
– The registration number in Republic of Moldova is 12595 (28.02.2008).

GUNA BOWEL acts as a protection of the intestinal epithelium, prevents intestinal dysbiosis, stimulates and corrects intestinal peristalsis, has a laxative effect in the treatment of irritable bowel syndrome, as well as choleretic action.
GUNA BOWEL was included in the regimen from the onset period of acute pancreatitis in children in the dosage of:

- Children under the age of 2 years, **3 drops, 3 times per day**.
- Children from 2 to 6 years, **5 drops, 3 times per day**.
- Children from 6 to 10 years, **10 drops, 3 times per day**.

The treatment duration was lasting one month.

RESULTS

All the patients were transported by ambulance to the Children's Department and hospitalized in the Gastroenterology or Intensive Care Department.
It should be noted that the most common precipitating factors of acute pancreatitis were: respiratory tract infections, and ENT pathology (tonsillopharyngitis, sinusitis, otitis, bronchitis, pneumonia), gastritis, gall bladder dysfunction, and nutritional factors.
The clinical picture was dominated by the following: pain, dyspeptic, asthenoneurotic syndromes and the syndrome of endogenous intoxication.

In patients during the onset of AP an improvement of HPL - earlier hexane compounds (16,76±0,29 U/mL, $p<0,001$), HPL-earlier isopranol compounds (14,3±0,21 U/mL, $p<0,001$), as well as the HPL- transient isoprene (8,83±0,17 U/mL) was found during the examination, which compared with the control group **confirms significantly the oxidative stress**, which contributes to the pancreas morphological structures damage and functional impairment.

A significant reduction of HPL- later hexane until (0,55±0,03 U/mL, $p<0,01$) compared with the control Group (2,08±0,52 U/mL), HPL- transient isoprene (8,83±0,17 U/mL, $p<0,001$), and later (1,4 ± 0,1 U/mL) followed by the reduction rates after the treatment was showed during the onset of the disease.

The MDA increase should be emphasized

Markers	Healthy Children I-Group (n = 20) p1	Children with AP during the onset II-Group (n = 40) p2	Children with AP received standard treatment + GUNA BOWEL 1 month III-Group (n = 30) p3	Children with AP received standard treatment 1 month IV-Group (n = 30) p4	p
HPL-hexan *early* uc/ml	13,93±0,43	16,76±0,29	15,84±0,53	13,03±0,06	$p_{1-2}<0,001$ $p_{1-3}<0,01$ $p_{3-4}<0,001$
HPL-hexan *interm* uc/ml	4,7±0,44	5,27±0,15	4,81±0,17	5,19±0,13	$p>0,05$
HPL-hexan *late* uc/ml	2,08±0,52	0,55±0,03	0,62±0,05	0,86±0,05	$p_{1-2}<0,01$ $p_{1-3}<0,01$ $p_{1-4}<0,05$ $p_{3-4}<0,01$
HPL-izopr *early* uc/ml	13,32±0,15	14,3±0,21	14,9±0,51	12,78±0,32	$p_{1-2}<0,001$ $p_{1-3}<0,01$ $p_{3-4}<0,01$
HPL-izopr *interm* uc/ml	10,36±0,17	8,83±0,17	9,31±0,53	8,32±0,25	$p_{1-2}<0,001$ $p_{1-4}<0,01$ $p_{2-4}<0,001$
HPL-izopr *late* uc/ml	1,6±0,16	1,4±0,1	1,55±0,25	1,61±0,2	$p>0,05$
DAM μM/l	15,32±0,64	18,96±0,99	17,14±0,47	18±0,9	$p_{1-2}<0,01$ $p_{1-3}<0,05$ $p_{1-4}<0,01$ $p_{2-4}<0,01$
AAT-hexan mM/s.l.	0,83±0,04	0,54±0,04	0,4±0,057	0,46±0,06	$p_{1-2}<0,001$ $p_{1-3}<0,001$ $p_{1-4}<0,001$
AAT-izopr mM/s.l.	3,25±0,22	3,93±0,25	3,62±0,59	3,06±0,37	$p_{1-2}<0,01$

TAB. 1

Oxido-reduction indicators system in children with acute pancreatitis (AP).

- the end product of lipids oxidation in patients with AP at the onset of the disease (18,96±0,99 nM/L, p<0,01) and after the treatment (18,0±0,9 nM/L, p<0,05), which seems to indicate the continuation of reparative processes in the gland.

Increased activity of HPL was associated with decreased levels of AOS-hexane (0,54±0,04 mmol / s.l., p<0,001) in children with AP as in the onset period and 1 month after therapy (0,46±0,06 mmol/s.l., p<0,001) compared with healthy children (0,82±0,04 mmol/s.l.).

Antioxidant serum was supported by the increase of AOS-isoprene in the initial stage of the disease (3,93±0,25 mmol/s.l., p<0,001) compared with healthy children (3,25±0,22 mmol/s.l).

The depletion of serum by AOS-hexane (0,46±0,06 mmol/s.l.) and HPL-isoprene. (3,06±0,37 mmol/s.l) antioxidant activity was revealed after the treatment (TAB. 1).

Nitric oxide (**NO**) is able to reinforce the negative effects of superoxide radical and

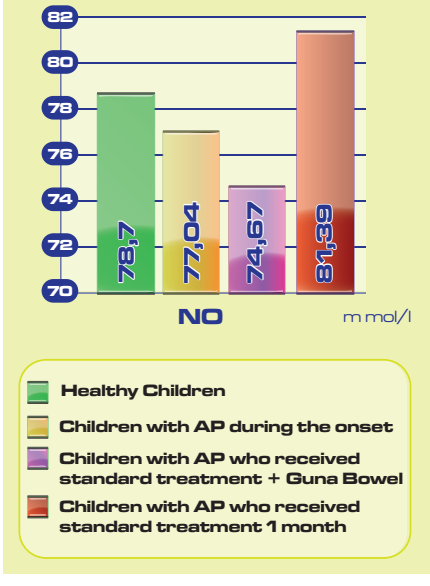

FIG. 1

Dynamics of nitric oxide (NO) concentration in the serum of children with AP.

other active oxygen species, whose role in the pathogenesis of toxic damage of the pancreas and the development of endotoxemia can be regarded as proven.
In the onset period a slight decrease NO (77,04±2,83 mmol/l) was observed, which is **more pronounced** 1 month after GUNA BOWEL treatment (74,67±6,34 mmol/l.).
In the indicators of NO in patients receiving standard therapy for 1 month we observed a slight increase (81,39±3,98 mmol/l) compared with healthy children (78,7±2,85 mmol/s.l.) (FIG. 1).

The next criterion for the excretory function disturbance of the pancreas and hyperamylasemia is hyperlipasemia, which is preserved at the end of the first week from the onset of the disease. The hyperamylasemia specificity increase should be considered significant in the enzyme increase 1,5-2 times higher than normal.
The hyperlipasemia indicators last longer than amylase activity in patients with AP.

During the onset of ETA average indices α-amylase (120,54±3,67 U/L) and lipase (67±1,29 U/L) were increased in comparison with the control group (healthy children) (α-amylase - 60,14±5,14 U/L and the lipase-43,4±1,34 units/L).
In patients from the III Group who received **GUNA BOWEL** for 1 month - there was a **significant reduction in α-amylase**-54,3±3,12 U/L and lipase - 52,12±1,68 U/L compared with patients enrolled in Group IV (α-amylase-72,94±2,43 U/L and the lipase-57,03±2,59U/L). (FIG. 2)

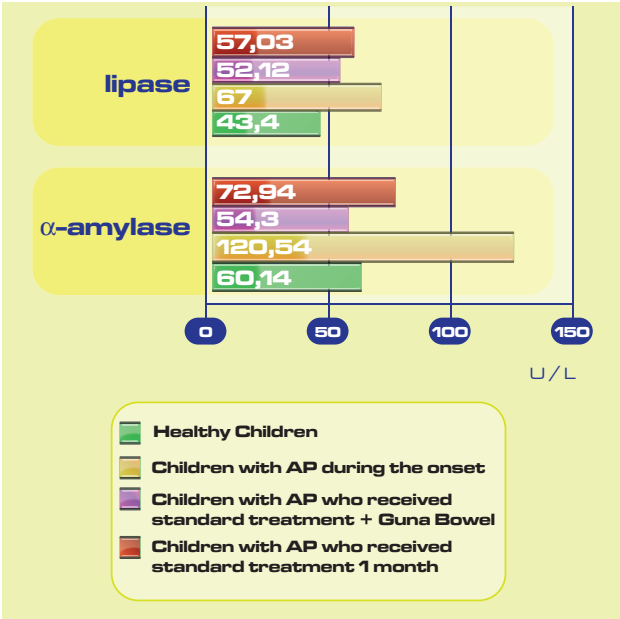

FIG. 2

Indicators of the excretory function of the pancreas (lipase, α-amylase).

Raising level of the proteolytic enzymes promotes catabolism, which contributes to EI symptoms, necrotic materials indicators.

Middle molecules affect the processes of life, causing intoxication, which is called "metabolic intoxication" by some authors. The level of middle molecules reflects the degree of abnormal protein metabolism and correlates the key of the clinical and laboratory prognostic criteria for metabolic disorders. The average molecules are also characterized by an index of toxicity in severe disease of the pancreas.
In children with AP during the onset of the disease the middle molecules concentration reached maximum values (22,58±1,57 mmol/s.l.) with a more rapid recovery in children from the Group III (14,66±0,6 M/s.l.) compared with the children who received standard treatment (17,89±1,36 mmol/s.l.) (FIG. 3).

Another indicator reflecting the endogenous intoxication syndrome is the concentration of necrotic substances.
The level of the necrotic substance was higher in children with ETA during the onset period (2,28±0,17 U/ml), which exceeded normal levels by 2-fold, with recovery to normal values after treatment with this drug after a month (1,46±0,07 U/ml) and patients who received standard treatment, we observed a slow decline (1,85±0,12 U/ml, p<0.05) (FIG. 4).

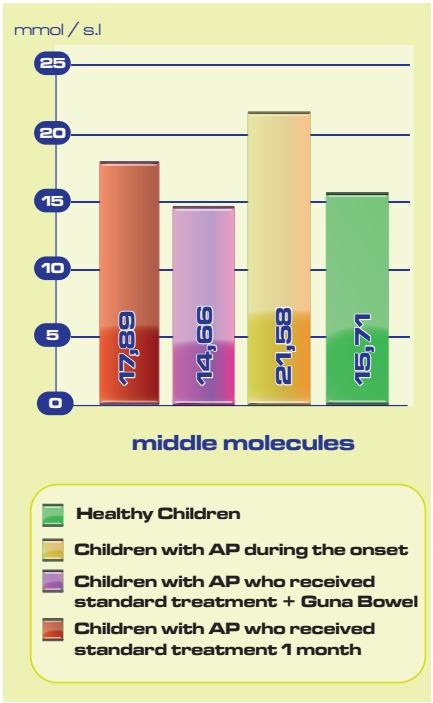

FIG. 3

Biological parameters of endogenous intoxication (middle molecules).

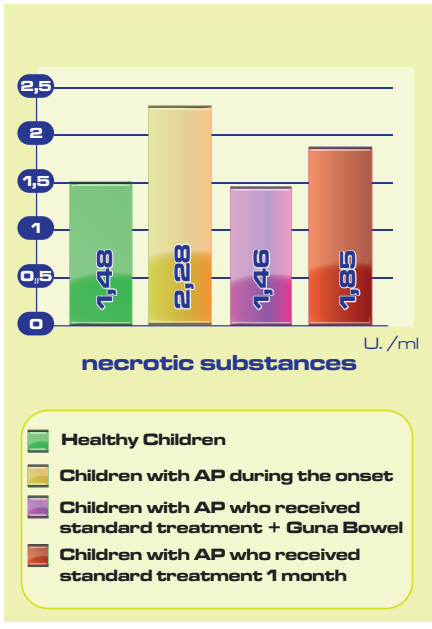

FIG.4

Biological manifestations of endogenous intoxication (necrotic substances).

The inclusion of **GUNA BOWEL** contributed to the normalization of the necrotic substances concentration (1,46).
In the children who received standard treatment the levels of necrotic substances remained elevated (1,85) (FIG. 4).

Thus, the introduction into therapy of GUNA BOWEL contributed to a more pronounced decrease in biological parameters of endogenous intoxication, stabilization of the excretory function of the pancreas, as well as oxi-redox system and NO.

CONCLUSIONS

1. These data prove the role of oxidative stress in the AP physiopathology, showing a significant increase in the serum of lipid peroxidation products - HPL with a subsequent decline to normal values after treatment.
The concentration of MDA is kept increased after the treatment too.

Compensation of oxidative stress is carried out by increasing the activity of HPL-isoprene in the period up to depletion of ETA's onset performance of antioxidant protection by the end of therapy.

2. The syndrome of endogenous intoxication in children with AP is characterized by increased concentrations of middle molecules in the period before the onset (22,58±1,77 U/Ml, $p<0.001$) and the restoration of normal values 1 month after the treatment with GUNA BOWEL.

3. The level of middle molecules is 1.4 times higher, and necrotic substances are 1.6 times higher compared with the same parameters in healthy children.

– The concentration of these substances reached the normal range in the patients who received GUNA BOWEL.

4. The introduction of GUNA BOWEL preparation in the standard treatment for children with AP contributes to a more rapid stabilization of oxi-redox system enzymatic biochemical disturbances, NO and endogenous intoxication. ■

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