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Adhesive diseases in children. Prevention, diagnosis and treatment strategies

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Abstract

Background: The adhesive disease and its associated complications, caused by adhesive mechanical bowel obstructions, mainly related to genetic causes and disorders of cell homeostasis, is one of the major health problems due to its diverse impact on the growing organism.
Material and methods: The clinical study was conducted on a group of 50 children aged 1 month – 18 years old with abdominal adhesion disorders, complicated by bowel obstruction, following a surgical intervention. Apart from the assessment of the anamnesis, clinical, and imaging manifestations, traditional bio-humoral homeostatic imbalance markers, endotoxemia levels, associated complications, and comorbidities, the blood inflammatory and excessive fibrosis biomarkers were assessed at different clinical periods of the pathological process.
Results: A non-randomized pro- and retrospective study was carried out to assess the epidemiological, clinical and paraclinical, histopathological, evolutionary, preventive and treatment charcteristics in order to determine the major complication triggers following a surgical intervention on the small intestine, colon, appendix or uterus , as well as to highlight their possible peculiarities in children.
Conclusions: This study completed the clinicians' views on intraperitoneal adhesion pathophysiology, thus confirming the importance of the microbial factor, inflammatory mediators, activation of humoral systems due to organic cellular lesions, the extension of the inflammatory response, as well as the genetic factors depending on the acetylation phenotype in children.
Key words: children, adhesive disease, diagnosis, treatment.

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Introduction

Adhesive disease and its complications, mainly caused by a mechanical bowel obstruction, is one of the major health problems due to its diverse impact on the growing organism [1, 2]. The high- incidence disability due to this pathology is still a topic under discussion. Currently, there is no unanimously accepted standard for the diagnosis, treatment and prophylaxis strategies in children. The actuality of this issue is determined by its high frequency, polymorphism of clinical manifestations, its severity and unpredictable evolution, poor prognosis, and associated complications. Recent studies have defined the long-lasting challenges related to this intra-abdominal complication. However, the latest successful researches in pathophysiology and molecular biology have opened new avenues in the assessment and prophylaxis of adhesion processes, by assessing the genetic factors, impaired cell metabolism and homeostasis that encodes the body's susceptibility to this complication [3, 4].

Adhesion formation is a risk factor following all the abdominal surgeries, occurring in up to 100% of cases. Adhesions are more commonly to occur after the surgeries performed on the small bowel, colon, appendix, or uterus. Adhesions are less common in surgeries on the stomach, bladder or pancreas. To date, there are no anatomical and clinical criteria to reduce postoperative complications, as well as there are no preventive measures to avoid adhesion processes, especially in children. The surgical diagnosis and management of abdominal diseases have an indisputable role in enhancing the early or supportive treatment. Despite some progress, there are still many questions, which arise the constant interest of the scientific world [5].

Additionally, a better understanding of the adhesion processes, which result in mixed bowel obstruction and might potentially evolve into multiple organ failure and intestinal failure, could help in developing a more effective approach in order to reduce complications, disabilities and the number of deaths. In the last decades, the nosological classification of adhesion processes has been carried out by describing their main clinical, imaging, histopathological and evolutionary patterns [6].

The purpose of the study. Complex clinical and paraclinical examination methods (biochemical, bacteriological, imaging, and histopathological assessment) were used to develop and optimize the diagnostic schemes, prognosis,

treatment, and prophylaxis in pediatric adhesive disease and its complications.

Material and methods

The clinical study was carried out at *Natalia Gheorghiu* Scientific Center of Pediatric Surgery, in collaboration with the Biochemistry Laboratory of *Nicolae Testemitanu* State University of Medicine and Pharmacy on a group of 50 children aged from 1 month to 18 years old, diagnosed with abdominal adhesion complicated by bowel obstruction, who underwent surgical interventions during 2011-2019. The research project was approved by the Research Ethics Committee of *Nicolae Testemitanu* State University of Medicine and Pharmacy (favorable opinion dated of 13.05.2015, minutes No 55). The anamnesis, clinical and imaging data, traditional bio-humoral homeostatic imbalance markers, endotoxemia levels, associated complications and comorbidities were assessed, as well as the following biomarkers: the level of nitric oxide (NO) metabolites and serum concentration of protein-bound hydroxyproline [7]; serum levels of interleukin 1β (IL-1β) via ELISA method, by using the "Imunoteh" test kit, USA; C-reactive protein (PCR) was estimated via the Beckman test kit, Ireland; the serum sialic acid (SA) and ceruloplasmin concentration was assessed via the photometric assay [8]; the intensity of the acetylation processes necessary to establish the acetylation phenotype was assessed by determining the N-acetyltransferase activity [9]; the serum copper level was determined via ELITEH test kit, France. The comprehensive extemporal biochemical assessment was performed in all patients from the study group, at different clinical and evolutionary pathological stages of the clinical course viz. inpatient and preoperative care, the 4th postoperative day, at time of discharge and follow-up period.

The morpho-histopathological assessment was carried out in 46 patients, who underwent a surgical intervention for intraperitoneal adhesions, in order to assess the prognosis, medical and surgical management, and prophylaxis of adhesive bowel obstruction. This study included macro- and microscopic examination of various abdominal adhesions, as well as in purulent peritonitis, acute appendicitis (catarrhal, phlegmonous, and perforated gangrenous), intra-peritoneal organ involvement, etc. The biopsy samples were retrieved from different anatomical sites, namely from occluded intestinal segments, mesentery, omentum, enterostomic portions, vermiform appendix, and intraperitoneal lymph nodes. Thus, the microscopic examination revealed fragments of bowel, omentum, adhesive bands, and vermiform appendix. The fragmented pieces had from 3-4 to 10 tissue sections. Tissue sections were stained with hematoxylin -eosin and picrofuxin by Van-Geison's method, whereas a 10% formalin solution was used to fix and study the samples under microscope with a 7 – eyepiece, using the 10x objective.

The test findings were evaluated via the Microsoft Office Excel program; the Student-test was applied to process the statistical mean values and Fisher criterion for coherent selections. To determine the statistical significance, the P value should have been less than 0.05 [10].

Results

The study included patients diagnosed with adhesive bowel obstruction. The non-randomized pro- and retrospective study was carried out to assess the epidemiological, clinical and paraclinical, histopathological, evolutionary, preventive and treatment peculiarities, as well as to determine the major complication triggers and their possible features with regard to currently available medical literature. The study group included 50 patients. Sex distribution pattern revealed a higher male to female ratio, viz. 2: 1. According to the place of residence, most children were from rural areas – 85% compared to those from urban areas – 15% of patients aged 6-12 years. The patients who were enrolled within the study were diagnosed with bowel obstruction, following a postoperative adhesive bowel obstruction and strangulation. These patients required a surgical intervention and were divided based on endotoxemia levels. Twenty patients, who suffered from adhesive bowel obstruction but showed successful conservative treatment outcomes, were excluded from the study.

Symptoms at admission included abdominal pain – 100%, intestinal motility disorders, dilated intestinal loops, hyperleukocytosis, intestinal transit disorders – 100%, vomiting – 100%, fever – 70%, tachycardia – 100%, tachypnea – 90%, etc. The time intervals from the onset and time of admission was 24-48-72 hours. Most children from the present study were hospitalized with severe and extremely severe abdominal adhesive pathological process, accounting for 42% of the total number of studied patients. Thus, 68% of patients were admitted with late clinical-evolutionary stages, later than 24-48-72 hours from the onset, which influenced the subsequent evolution, prognosis and the disease-specific survival rate.

It should be mentioned that patients with intraperitoneal inflammatory processes, hospitalized within the first 24 hours after the disease onset made up 58% of cases, over 36 hours – 24%, and over 2-7 days – 10%. Two patients underwent relaparotomy on the 5th postoperative day, followed by inter-intestinal band excision.

A severe disease onset was reported in 92.6% of cases, manifested by abdominal pain syndrome in 82.5% of cases, nausea and repeated vomiting episodes – 70%, insomnia – 58%, and anorexia – 70%. Constipation was present in 47% of patients aged over 3 years old and 26% of patients showed no changes in bowel movement frequency and transit patterns. 27% of patients had loose stools, thus being hospitalized within the Intestinal Disease Units in 9% of cases. 4% of children aged up to 3 years, were primarily diagnosed by the family doctor as experiencing a reaction to teething. These children were admitted at the late stages of the disease at specialized Surgery Departments.

54% of patients exhibited mild abdominal pain due to

the underlying acute respiratory viral infection, thus being late referred to surgery departments. 90% of patients had local peritoneal signs (muscular defense, abdominal bloating, lack of intestinal transit, etc.). Abdominal asymmetry was present in 49% of patients with intraperitoneal pain syndrome, whereas 18% of cases had a specific tense abdomen, 90% – positive peritoneal signs, 39% – different endotoxemia levels (fever, hyperemia, tachypnea, impaired skin microcirculation; 12 children showed a confusional state related to primary central nervous system (CNS) involvement and clinical features of a systemic infection, hemodynamic changes and homeostasis; 8 children exhibited coagulopathy with bleeding manifestations (systemic hemorrhage and thrombocytopenia).

Paraclinical examinations revealed hyperleukocytosis in 88.8% of patients, leucopenia – 16.4%, thrombocytopenia – 10.2%, an increased ESR – 86.2%, anemia – 66.6 %, hypoproteinemia and dysproteinemia – 71.2%, hypertransaminasemia – 20.1%, low prothrombin index – 74.4%, high fibrinogen concentration – 58.6%, and hydroelectrolytic disorders were found in 91.1% of patients. Imaging scans included abdominal ultrasound exam, barium sulfate contrast of gastrointestinal (GI) transit time, computed tomography (CT) (in 5 patients), which allowed to diagnose a positive intestinal obstruction.

Acetylation phenotype was determined in all 50 patients. The studies revealed that of the 50 patients, who underwent clinical and biochemical assessment, 32 (65%) patients exhibited fast acetylators, whereas 18 (35%) – slow acetylators.

Some biochemical and immuno-biochemical changes were particularly highlighted in children with different acetylation phenotypes.

The findings presented in table 1 show that the nitric oxide (NO) metabolite level was significantly higher at admission time, thus exceeding 3-10 times the control values. At the same time, the highest NO values were recorded in adhesive processes, following an apendicectomy, as well as in fecal peritonitis (almost 10 times higher compared to that of the control group). However, this index gradually decreased on the first day postoperatively and subsequently, showing its minimum values of 2.2-2.8 times higher compared to the control group, which is considered as a reference range for the 9th-10th day of hospital discharge.

Similar, though milder changes were recorded in dynamic assessment for serum cytokine IL-1β, the data obtained (tab. 2) showed that serum IL-1β concentration was significantly higher at admission, viz. exceeding 3-7 times the control group values. At the same time, the highest serum IL-1β values were recorded in adhesive processes in fecal peritonitis and in intraperitoneal adhesive processes (almost 7 times higher compared to that of the control group). However, this index gradually decreased on the 1st day postoperatively and subsequently, the minimum values exceeding 1.6-2.1 times higher than the control group indices, which is considered as a reference range for the 9th-10th day of hospital discharge.

The serum C-reactive protein (CRP) level increased significantly at admission time, exceeding 4-12 times the control values and maintained high values on the 1st and 3rd day postoperatively. However, it gradually decreased on the 5th day postoperatively, whereas at discharge, the CRP level was 1.4-2.6 times higher than the reference values, though showing no statistical relevance (tab. 3).

Table 1

Dynamic alterations of serum nitric oxide metabolites levels (NO, μmol / l) in abdominal adhesive processes of different origin

Research stages	Disease types				
	A. Acute phlegmonous appendicitis	B. Adhesive processes after appendicectomy	C. Adhesive processes in fecal peritonitis	D. Adhesive bowel obstruction	E. Intra-peritoneal adhesions
At admission	2.1 ± 0.36** 280%	7.4 ± 1.12** 987%	8.1 ± 0.95*** 1080%	4.3 ± 1.02** 573%	3.1 ± 0.44*** 413%
1st day, postoperatively	2.9 ± 0.56** P_1>0.5 387%	6.3 ± 1.14** p_1>0.5 840%	7.4 ± 0.86*** p_1>0.5 987%	4.5 ± 0.89** p_1>0.5 600%	3.7 ± 0.41*** p_1>0.5 493%
3rd day, postoperatively	3.5 ± 0.81** p_1<0.05 467%	3.8 ± 0.45*** p_1<0.01 507%	8.5 ± 0.72*** p_1>0.5 1138%	3.6 ± 0.45** p_1>0.5 480%	3.1 ± 0.46** p_1>0.5 413%
5th day, postoperatively	1.7± 0.09** p_1>0.5 227%	2.1± 0.38** p_1<0.01 280%	7.3 ± 0.31*** p_1>0.5 973%	2.3 ± 0.51** p_1>0.5 307%	2.8 ± 0.37** p_1>0.5 373%
At discharge	2.1 ± 0.32** p_1>0.5 280%	0.94± 0.17 p_1<0.001 125%	1.86 ± 0.24** p_1<0.001 248%	1.3 ± 0.42 p_1<0.05 173%	1.7 ± 0.29* p_1<0.05 227%
Control group	0.75 ± 0.08 100%	0.75 ± 0.08 100%	0.75 ± 0.08 100%	0.75 ± 0.08 100%	0.75 ± 0.08 100%

Note: Statistical significance if compared to control values - * - p <0.05; ** - p <0.01; *** - p <0.001; if compared to the 1st stage - p_1<0.05; p_1<0.01; p_1<0.001.

Table 2

Dynamic alterations of serum cytokine IL-1β levels (μg / l) in abdominal adhesive processes of different origin

Research stages	Disease types				
	A. Acute phlegmonous appendicitis	B. Adhesive processes after appendicectomy	C. Adhesive processes in fecal peritonitis	D. Adhesive bowel obstruction	E. Intra-peritoneal adhesions
At admission	44.6 ± 6.81* 231%	98.4±10.26** 510%	136.4 ±11.35*** 707%	75.1 ± 12.27* 389%	131.7 ± 10.71** 682%
1st day, postoperatively	57.9 ± 7.53** p_1>0.5 300%	101.2 ± 11.82*** p_1>0.5 524%	118.6 ± 8.72*** p_1>0.5 615%	87.5 ± 10.34** p_1>0.5 453%	140.4 ± 18.12*** p_1>0.5 727%
2nd day, postoperatively	48.1 ± 6.81* p_1>0.5 249%	91.7 ± 9.75** p_1>0.5 472%	89.4 ± 6.91** p_1<0.01 463%	75.6 ± 8.91** p_1>0.5 392%	108.1±11.87*** p_1>0.5 560%
5th day, postoperatively	34.1 ± 9.17 p_1>0.5 177%	40.1 ± 6.68* p_1<0.01 208%	52.7 ± 5.86** p_1<0.001 273%	55.2 ± 10.13* p_1>0.5 286%	58.6 ± 14.21* p_1<0.01 294%
At discharge	26.5 ± 5.84 p_1>0.5 173%	31.1 ± 3.11 p_1<0.05 161%	31.7 ± 2.42 p_1<0.001 164%	40.7 ± 9.77 p_1<0.05 211%	32.8 ± 10.35 p_1<0.001 170%
Control group	19.3 ± 4.5 100%	19.3 ± 4.5 100%	19.3 ± 4.5 100%	19.3 ± 4.5 100%	19.3 ± 4.5 100%

Note: Statistical significance if compared to control values - * - p <0.05; ** - p <0.01; *** - p <0.001; if compared to the 1st stage - p_1<0.05; p_1<0.01; p_1<0.001.

Table 3

Dynamic alterations of serum C-reactive protein (CRP) level (mg / l) in abdominal adhesive processes of different origin

Research stages	Disease types				
	B. Acute phlegmonous appendicitis	C. Adhesive processes after appendicectomy	D. Adhesive processes in fecal peritonitis	E. Adhesive bowel obstruction	F. Intra-peritoneal adhesions
At admission	20.2 ± 4.36** 388%	41.7±8.16*** 802%	62.0±7.83** 1192%	9.8±2.43 188%	29.3±8.72** 563%
1st day, postoperatively	25.1 ± 5.74** p_1>0.5 419%	36.9±6.72*** p_1>0.5 710%	54.3±5.6*** p_1>0.5 1044%	25.3±7.51* p_1<0.05 710%	38.5±6.92*** p_1>0.5 740%
2nd day, postoperatively	21.8 ± 3.78** p_1>0.5 419%	29.1±5.89** p_1>0.5 560%	37.8±4.86** p_1<0.05 727%	19.7±4.12** p_1<0.05 302%	36.1±9.16** p_1>0.5 694%
5th day, postoperatively	12.4 ± 3.06* p_1>0.5 238%	15.7±5.36** p_1<0.05 302%	18.1±2.31** p_1<0.001 348%	14.7±7.34 p_1>0.5 348%	16.7±5.36** p_1>0.5 321%
At discharge	10.7 ± 6.91* p_1>0.5 206%	13.4±7.26 p_1<0.05 258%	9.7±1.16* p_1<0.001 187%	7.2±2.33 p_1>0.5 138%	12.3±6.58 p_1>0.5 237%
Control group	5.2 ± 0.1 100%	5.2±0.1 100%	5.2±0.1 100%	5.2±0.1 100%	5.2±0.1 100%

Note: Statistical significance if compared to control values - * - p <0.05; ** - p <0.01; *** - p <0.001; if compared to the 1st stage - p_1<0.05; p_1<0.01; p_1<0.001.

Alterations in serum sialic acids and protein-bound hydroxyproline (tHP) levels in children with dynamic adhesion processes, depending on acetylation phenotype and treatment approach are shown in Table 4. Therefore, the levels of sialic acids and tHP at admission and on the 1st day postoperatively were significantly higher than those from fast-acetylators control group. However, this index decreased on the 3rd day postoperatively, having its minimum values on the 9th-10th day, at discharge. A similar dynamic pattern was recorded for slow acetylators, although the serum sialic acids and tHP levels were lower than in fast acetylators, whereas the highest concentration was recorded on the 1st day postoperatively, which decreased to normal values at the time of discharge (tab. 4).

The serum copper concentration in slow acetylators showed a statistically significant increase in the early stages, having the highest values on the 5th day postoperatively, followed by a decrease on the 10th -15th day, at discharge (tab. 5). The serum copper level in fast acetylators increased on the 1st postoperative day, then decreased to its lowest values on the 5th day postoperatively and afterwards returned to its control values.

The level of ceruloplasmin, a copper-containing protein in slow acetylators elevated after surgery, showing the hi-

Table 4

Dynamic alterations of serum sialic acid and protein-bound hydroxyproline (tHP) levels in children with serum abdominal adhesive processes of different origin, depending on acetylation phenotype and treatment approach

Indices	Serum sialic acid level		Serum protein-bound hydroxyproline (tHP) level	
Research stages	Slow acetilators	Fast acetilators	Slow acetilators	Fast acetilators
At admission	3.2±0.18*** 152%	3.5±0.21*** 167%	131.7±6.54* 122%	136.9±8.42* 126%
1st day, postoperatively	3.8±0.25** 181% p>0.5	3.9±0.28** 186 % p>0.5	139.8±10.82* 129% P>0.5	161.1±15.47** 149% p>0.5
3rd day, postoperatively	3.7±0.17*** 176% P>0.5	3.4±0.19** 162% P<0.05	116.8±11.47 117% P>0.5	136.5±12.02* 126% P>0.5
5th day, postoperatively	2.3±0.21 114% P<0.05	2.5±0.19 119% P<0.05	98.9±7.82 110% P<0.05	112.2±7.31 122% P>0.5
At discharge	2.2±0.11 100%	2.3±0.17 114%	102.3±7.15 110%	110.3±8.12 119%
Control values	2.1±0.19 100%	2.1±0.19 100%	108.3±6.18 100%	108.3±6.18 100%

Note: Statistical significance if compared to control values - * - p <0.05; ** - p <0.01; *** - p <0.001; if compared to the 1st stage - p_1<0.05; p_1<0.01; p_1<0.001.

Table 5

Dynamic alterations of serum copper and ceruloplasmin levels in children with serum abdominal adhesive processes of different origin, depending on acetylation phenotype and treatment approach

Indices	Serum copper level, μM/l		Serum ceruplasmin level, mg/l	
Research stages	Slow acetilators	Fast acetilators	Slow acetilators	Fast acetilators
At admission	27.1±2.1* 132%	25.4±2.4 124% p>0.5	377.3±26.8 107%	381.3±28.9 108% p>0.5
1st day, postoperatively	38.6±3.4** 188%	36.1±3.8** 176% p>0.5	446.5±25.6 126%	397.6±41.2 112% P<0.05
3rd day, postoperatively	32.7±4.1** 160%	33.1±2.4** 161% p>0.5	380.7±19.8 108%	371.3±25.7 105% p<0.05
5th day, postoperatively	31.2±4.1* 152%	23.8±2.1*** 116% p>0.5	368.3±21.2 104%	361.5±19.7 102% p<0.05
At discharge	24.8±3.1 121%	22.7±2.4 111% p>0.5	363.8±24.6 103%	359.4±21.9 101% p>0.5
Control values	20.5±1.4 100%	20.5±1.4 100%	354.1±22.7 100%	354.1±22.7 100%

Note: Statistical significance if compared to control values - * - p <0.05; ** - p <0.01; *** - p <0.001; if compared to 1st stage - p_1<0.05; p_1<0.01; p_1<0.001.

Table 6

Bacteriological study

Microbial flora	Bacterial agent	Abs.	P±ES,%
Gr. -	E. coli	25	50±5.4%
	Ps. Aeroginosa	5	10±1.2%
	Kl. Pneumonae	7	14±2.9%
	Proteus	4	8±1.4%
Gr. +	St. aureus	13	26±1.7%
	Str. Epidermidis	8	16±0.4%
	Candida albicans	10	20±2.8%
	Intestinal dysmicrobism, grade I-IV	30	60±5.7%
	2 bacterial association	12	24±1.3%
	3 bacterial association	18	36±0.8%
Anaerobes	Clostridium	5	10±0.8%
	Antibiotic-resistant strains	8	16±1.8%

ghest values on the 5th day postoperatively, then returned to normal ones at discharge. In fast acetylators, the dynamics of ceruloplasmin was similar to that of slow acetylators, howe-ver, being statistically irrelevant (tab. 5).

The bacteriological studies were carried out according to the developed algorithm and the study design, presented in table 6, followed by the diagnosis and monitoring of the bacterial flora within the abdominal cavity, blood and wound. The results showed a predominance of Gr. Flora - 50% and polybacterial associations – 60%.

Thus, patients with diffuse purulent-fibrinous peritonitis that was related to an underlying long-lasting and persistent intestinal paresis, developed grade I-III dysbiosis soon after surgery, being determined at all levels of GI tract. The following pathogens were reported in 3 patients aged 2-5 years with ileo-stomata: enteroccocus and Klebsiela strains. The prophylaxis of intestinal dysbiosis was corrected via selective decontamination methods that included probiotics (Linex, Opefera, Acidolac, Lactobex Baby). A reduced pathogenic population and small amounts of lactobacteria

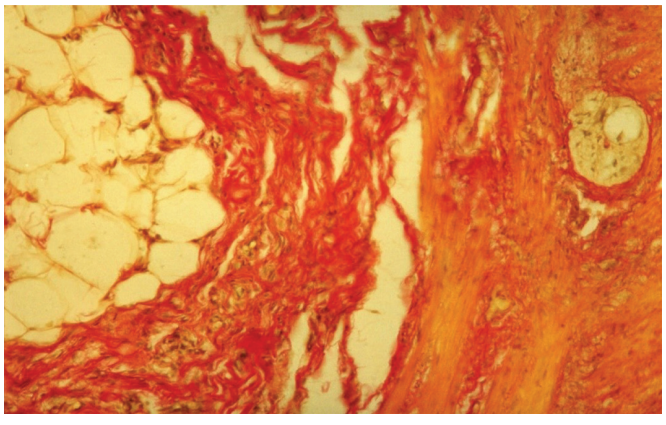

Fig. 1. Productive perivisceritis evolving into sclerosis, collagen fiber bundles with solitary fibrocytes. Van Gieson staining. 10-x eyepiece, 20-x objective.

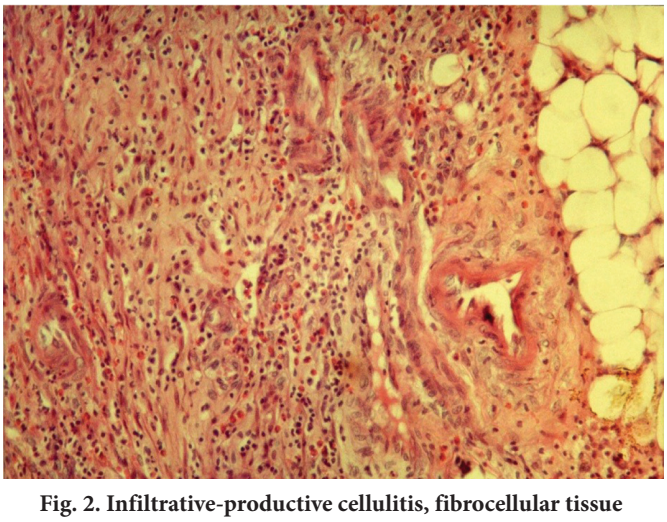

Fig. 2. Infiltrative-productive cellulitis, fibrocellular tissue with solitary or group lipocyte inclusions. Hematoxylin-eosin staining. 10-x eyepiece, 20-x objective.

allowed optimizing the time of stromal closure, which was performed on the 2nd and 4th month after the application. This therapeutic approach along with antiadhesion drugs (Serrata, Longidaza 3000ME, rectal suppositories, Cuprinil per oral, Fermencol – electrophoresis and local gel, as well as the use of anti-inflammatory and immunomodulatory medication – Wobenzym) allowed optimizing the stromal closure time that was performed on the 2nd and 4th month after their application by latero-lateral (2) and termino-terminal (1) anastomoses, followed by positive treatment outcomes at early and late stages. The children were aged from 2.3-5 years old.

Microscopic histopathological assessment of the biopsied material revealed presence of celluloid fat, crossed by intermediate layers of connective tissue, divided into irregular-sized cellulo-adipose lobules, often round or oval-shaped. The connective spaces between the cellulo-adipose lobules varied in thickness, being made up of connective fibers that were parallel to a significant number of fibrocytes (fig. 1 and 2).

There was found a number of areas with swollen and homogenized connective fibers, located within a homogenized ground substance with the high number of fibrocytes. The blood vessels were unevenly dilated and hyperemic. The cellulo-adipose tissue that was adjacent to the infiltration areas exhibited an increased concentration of fibroblasts (massive leukocyte infiltraion), which proliferated from the connective spaces. The analysis of the obtained findings regarding the small bowel portion, severe inflammatory changes of the peritoneum and intraperitoneal organs, as well the high level of body sensitivity to determine the inflammation degree was carried out. Subsequently, a more in-depth study was performed on the biopsy samples of the intraperitoneal adhesions, retrieved from the same anatomical and pathological sites, as well as on the neuronal damage of the Auerbach plexus.

Most of hospitalized children with abdominal adhesions were admitted with severe or extremely severe health condition that made up 71.5% of all patients included within the study group. According to the research data, 78.9% of patients were hospitalized in late clinical evolutionary stages, which had an extremely negative impact on further evolution and the prognosis of the disease.

It should be noted that a significant number of children (70%) were reported with concomitant cardiovascular, respiratory, renal-urinary, and musculoskeletal disorders, diabetes mellitus, acute mesadenitis, phlegmonous diverticulitis, Flexner dysentery, hemorrhagic vasculitis, parasitic diseases (enterobiosis, ascariosis, and hydatidosis), post-traumatic sequelae, etc.

Antiadherent treatment. The complex antiadherent treatment was started intraoperatively with a mild adhesiolysis, peritoneal cavity lavage, 200 ml of 5% aminoapronic acid solution intraperitoneally + 2 ampoules of thrombin and abdominal cavity drainage with glove lamellae in the right iliac fossa.

The antiadherent treatment approach included collagen synthesis inhibitors – Cuprinyl-penicillamine and bacterial collagenase – *Clostridiopeptidase A* for removing collagen fiber formation. Penicillamine was administered from the 2nd-3rd day postoperatively, doses were based on the child's age: 0.15 / 1 capsule – in children up to 5 years, 0.3 / 2 capsules – in children aged from 5 to 12 years old and 0.4 / 3 capsules – over 12 years, once / per day. The treatment lasted from 10-14 days. No side effects were reported regarding the use of penicillamine.

Clostridiopeptidase A was used as ultrasonophoresis with iruxol, a combination of clostridiopeptidase A and chloramphenicol. Ultrasonophoresis with iruksol was applied on the anterior abdominal wall on the 2nd-3rd day after surgery. The ultrasound UTP-1 device used a pulsating mode, at one pulse /second frequency and 0.4 W / cm intensity. The course of treatment included up to 10 procedures.

Children with adhesive intestinal obstructions, who underwent laparotomy, were given postoperative treatment on the 1st-2nd day by using electrophoresis or collalizine injections nearby the plague, followed by galvanization, instead of ultrasonophoresis+iruksol.

The antiadherent treatment scheme also included Fer-

mencol, containing a series of highly active collagenases that enabled the hydrolysis of both collagen peptide bonds and polysaccharides that form the connective tissue. 15 procedures of electrophoresis with Fermencol gel were applied on the postoperative wound. Longidase 3000ME with immunomodulating and collagenolytic effects was also applied.

Treatment of adhesive syndrome. The complex treatment approach of the adhesive syndrome was developed at Natalia Gheorghiu Scientific Center of Pediatric Surgery, IMPH IMC that included the following major principles:

- Food intake suppression;
- Rebalance of the hydroelectrolytic, acid-base, and metabolic disorders under constant and individual monitoring;
- Use of related detoxification methods (plasmapheresis);
- Antibacterial therapy;
- Immunocorrection therapy;
- Surgical treatment;
- Relapse prevention.

According to the assessed changes, the minimal resuscitation treatment was based on the following complex investigations: clinical, imaging, biochemical, and bacteriological tests, leukocyte intoxication index, etc., thus justifying the following therapeutic algorithm in the preoperative stage (to reduce the endogenous intoxication and improve critical organ functioning, particularly of the GI tract):

- Rebalancing of hydroelectrolytic and metabolic disorders;
- Anemia correction;
- Antibiotic therapy in providing resolution of the infectious process (cerulopasmine, aminoglycosides, metronidazole, etc.);
- Use of hepatoprotective agents;
- Gastric and bowel decompression;
- Fever treatment;
- Symptomatic medication (vasoactive, corticosteroid, and cardiotonic drugs).

The most appropriate rebalancing approach was surgery, followed by patient detoxification and fast recovery. The surgical method of choice and its duration depends on the diagnosed condition, the evolutionary stage, complications, the patient's biological field, etc.

Tactical and technical aspects of surgical interventions / repeated interventions were aimed:

- To undergo repeated laparotomy or relaparotomy with peritoneal cavity drainage using glove lamellae;
- Adhesiolysis;
- To remove obstruction of the GI tract and provide proper bowel movement;
- To restore the digestive tract integrity by applying intestinal anastamosis (term-terminal, termino-lateral, and latero-lateral);
- To eliminate the source of peritoneal contamination and restore the abdominal cavity.

To achieve these purposes, a primary surgery or a repeated laparatomy is required, the latter could be performed via the surgical or median approach. Previous laparotomy was considered as the optimal access pathway.

The postoperative treatment is based on the following objectives:

- Nasogastric intubation (reduces abdominal distension, avoids repeated vomiting and prevents from entering into the upper respiratory tract, improves pulmonary ventilation);
- Oxygen therapy in patients with clinical signs of respiratory failure;
- Clinical and biological follow-up and specific treatment adjustments;
- The preoperative antibiotic therapy is continued based on clinical criteria, then modified depending on the antibiotic-susceptibility testing results;
- Stimulation of intestinal peristalsis (Prozerini, Cerucal, and Quamatel IV solution);
- Selective decontamination (Linex, Opefera, Acidolac, Probiotic, Lactobex Baby, Ferzim plus, AERIS, etc.);
- Hydroelectrolytic and metabolic rebalancing;
- Early patient mobilization;
- Hygiene and dietary regimen aimed to resume the patient's natural diet;
- Patients' local evolution (peritoneal, abdominal) and overall condition follow-up;
- Hemodynamic monitoring (pulse rate, respiration, temperature, blood pressure, central venous pressure, diuresis, etc.);
- Immunocorrection therapy by using amino acids, which increase protein synthesis and decrease proteolysis, as well as administration of essential polyene fatty acids Omega3, Fish Oil Jr;
- Antiadherent treatment according to the developed schemes and symptomatic medication;
- Plasmopheresis, if required.

The most difficult stage of the above mentioned treatment approach is the antibacterial one, due to its long-lasting antibiotic administration (before surgery), followed by the formation of antibiotic-resistant strains, high virulence of microbial agents against the underlying low-level resistance of the growing body, detection of microbial associations, and higher incidence of allergic reactions. Preoperative patient preparation for improving and restoring vital functions should not last less than 2 hours and not exceed 6 hours.

Discussion

The study was based on a complex multi-planar analysis of clinical observation data, comprehensive laboratory and imaging methods, morphology, mathematical assessment of marker indices in basic pathologies, as well as on medical and surgical treatment outcomes in 50 children aged from 1 month -18 years old, who underwent abdominal surgery.

It should be mentioned that all children were diagnosed via minimally invasive methods, namely, X-ray, imaging, and laboratory investigations, taking into account their medical history, type of surgical intervention, primary dis-

ease, and previous abdominal surgeries, in order to find the best treatment solution in terms of the type, clinical picture, clinical and evolutionary stage, and acute phase patterns of the disease. Since suspected complications are the first information-gathering step of the diagnostic process, all patients with abdominal surgical infections require a careful medical interviewing. Moreover, most apparently irrelevant details related to less specific clinical manifestations and minimal changes found in usual investigations might be essential for establishing an early effective diagnosis and prevention, as well as justify an adequate treatment, based on currently available and accepted disease diagnosis, prevention and management [11, 12].

As regarding the pathology-related problems, they arose from numerous factors involved in the etiopathogenesis of these pathological conditions, which might cause major changes in different homeostatic systems of the growing body [13].

It should be noted that further studies are required to assess the risk factors, in order to develop specific preventive measures and a differentiated individualized treatment [14, 15].

The comprehensive study of the anamnestic data regarding the basic condition and its associated complications allowed concluding that the clinical features were characterized by an acute onset and various clinical symptoms. It should also be mentioned that the severe patient's condition developed considerably on a previously underlying disorder, which made it difficult to properly assess the child's condition. Furthermore, most patients had previously undergone surgical treatment in the late stages of destructive acute appendicitis and appendicular peritonitis, which, apart from challenges in establishing the primary diagnosis and medical-surgical approach, contributed significantly to being associated with complications or conditions that required relaparatomy.

The development of complications is mainly due to the late diagnosis of acute appendicitis, errors in the medical and surgical treatment of intestinal obstruction, inadequate clinical and evolutionary assessment of peritonitis, inadequate abdominal cavity drainage, and inappropriate use of enterostomal therapy, which resulted in adhesion development, long-lasting tertiary peritonitis, etc., a fact being reported by a number of authors [16].

Patients enrolled within the study had a precarious biological field due to various causes and associations, as well as a clinical picture, characterized by an acute onset, severe signs of endotoxicosis (grade II-III), endotoxic shock, peritoneal sepsis, fever, chills, etc. Moreover, the severe child's condition largely developed on an underlying pathology, thus making it difficult to assess the clinical and evolutionary stages of the disease. Most patients exhibited severe fecal peritonitis, perforated gangrenous appendicitis, and intestinal obstruction (both mechanical bowel obstructions and intestinal invagination). These children had signs characteristic of endogenous intoxication, septic and toxic shock, and severe microcirculatory disorders, followed by multiple organ failure.

The obtained findings indicated that the main sources of endogenous intoxication in generalized intra-abdominal infections are both the large peritoneal surface and the GI tract pathology, in case of intestinal failure. The endogenous infection of the patient with generalized peritonitis showed a "primary endogenous" character, thus contributing to selective decontamination of the digestive tract in patients with peritonitis and abdominal sepsis. Therefore, the bacteriological assessment is crucially important for all stages of acute peritonitis management in children, namely in the diagnosis, postoperative antibacterial treatment and early diagnosis of postoperative complications based on the developed algorithm.

Recent studies have provided increasingly more evidence on the importance of intestinal microbiota in the pathogenesis of peritonitis and in the onset of the adhesive diseases. This topic was given special attention since intestinal microbes might play a key role in the development of infants and their immune system due to the immunological, metabolic and neurological benefits offered to the growing body. The specialized literature has reported that intestinal microflora and intestinal microbes are essential for the normal development of the child, since these help in food digestion, vitamin K and B12 production , metabolism of xenobiotics, anti-pathogen protection, stimulation or modulation of the immune system , as well as provide control over the hypothalamic pituitary adrenal axis [17].

The imbalance of the normal gut microbiota, also called dysbiosis, can lead to gastrointestinal disorders, such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and different systemic manifestations, such as blood clotting and nerve conduction disorders due to vitamin K and B12 deficiency. There are evidences suggesting that several intrinsic and extrinsic factors, such as genetic variation, diet, stress, and medications, particularly antibiotics, can dramatically interfere with gut microbiota, resulting in abdominal dysbiosis [18, 19]. It has been proven that the imbalance of the normal gut microbiota, dysbiosis, and the immune response of the associated mucosa play a key role in the development of inflammatory bowel disease (IBD), peritoneal inflammation, endogenous intoxication, and abdominal and systemic sepsis, being obviously involved in the intimate pathogenic, pathochemical and immunobiochemical mechanisms of excessive fibrous tissue formation, thus in developing adhesive diseases among children [20].

Complicated evolution of acute peritonitis is often caused by both multifactorial association of the bacterial agents and the antibiotic-resistant strains that increase the incidence of postoperative complications, which require new conceptual approaches and decision-making attitudes [21, 22].

There are current studies that prove the benefits of therapeutic strategies for managing intestinal dysbiosis via administration of antibiotics, prebiotics, probiotics and fecal microbiota transplantation for IBD [23].

The concomitant disorders found in children, increased the risks associated with anesthesia, surgery, and postoperative accidents and complications, thus resulting in costly treatment and poor prognosis. Therefore, there is a stringent need to identify the main approaches in prevention of

adhesive diseases in order to minimize the financial impact on healthcare systems [24].

Currently, it is highly important to improve the study aspects related to disease pathogenesis, predicting factors for developing abdominal adhesion formation and differentiated treatment approaches [25]. Therefore, it is worth mentioning that changes found in complete blood count and routine plasma biochemical markers (total protein level and fractions, liver function tests, blood coagulation tests, ionogram data) of the patients included within the study helped to assess the severity degree of total fecal and purulent peritonitis, intestinal obstructions, spontaneous intestinal fistulas, perforated gangrenous appendicitis in advanced clinical and evolutionary stages. The bacteriological investigations allowed monitoring the main causative pathogens of intestinal adhesive disease.

Following the analysis of pre- and retrospective study data, based on patient's medical observation records, surgical protocols and investigation data, including specially developed study aassessment of molecular mediators of intestinal fibrosis (inflammation markers – NO, IL-1β, CRP, sialic acid, protein-bound hydroxyproline, ceruloplasmin, and serum Copper levels) in children with different acetylation phenotypes. The peculiarities of these changes were also established.

An increased serum nitric oxide (NO) level relates to the presence of an acute inflammatory process that might produce the abdominal adhesion formation. NO plays a crucial role in synthesizing from L-arginine by nitric oxide syntheses (NOSs). NO involves immune responses via cytokine-activated macrophages, which yield high NO levels. Selective NO biosynthesis inhibitors and synthetic arginine analogues have been reported to treat NO-induced inflammation [26].

The present study showed a sudden increase in serum IL-1β values at admission, with the highest levels being recorded in fecal peritonitis and intra-peritoneal adhesive processes, which later on gradually decreased due to the treatment applied, thus having minimum values at time of patient's discharge. Elevated serum IL-1β values suggest the presence of an acute inflammatory process, which is responsible for abdominal adhesion formation. IL-1β, also known as leukocyte pyrogen, endogenous leukocyte mediator, mononuclear cell factor, and lymphocyte activation factor, is an important mediator of variety of cell activities, including cell proliferation, differentiation, and apoptosis. [27]. Induction of cyclooxygenase-2 (PTGS2/COX-2) by this cytokine in the central nervous system (CNS) is found to produce inflammatory pain hypersensitivity. [28]. The excessive IL-1 production is harmful and contributes to developing inflammatory diseases, autoimmune encephalomyelitis, rheumatoid arthritis, gout and other disorders. [29]. It has also been suggested that the release of IL-1β, mediated by inflammasomes, might be a strictly cytolysis-induced event due to necrosis or pyroptosis. Pyroptosis or caspase 1-dependent cell death is initiated by a cascading activation of inflammasomes, which leads to the release of IL-1β [30].

The C-reactive protein (CRP) marker of acute inflammatory response was also assessed within the research, showing significantly higher values in the clinical and evolutionary stages of the pathological process. Moreover, the high values found in the early research stages, although slowly decreasing due to the treatment applied, were still elevated at time of discharge in both post-apendicectomy adhesive processes and fecal peritonitis, thus indicating the persistence of an inflammatory process. CRP is produced as a homopentameric protein, termed native CRP (nCRP) predominantly in liver hepatocytes, but can also be synthesized by smooth muscle cells, macrophages, endothelial cells, lymphocytes and adipocytes. nCRP can dissociate at sites of inflammation and infection into five separate monomers, termed monomeric CRP (mCRP). CRP plays an important role in inflammatory processes and hosts responses to infection, including complement pathway, apoptosis, phagocytosis, nitrogen oxide (NO) release, and cytokine production, primarily of interleukin-6 and TNF-α [31]. Therefore, the level of serum CRP reflects the intensity of abdominal inflammatory processes in children with adhesion processes.

Sialic acids are involved in different biological events, such as cell adhesion, immunity and inflammation, while the increasing cellular inflammatory responses due to sialic acids removal from ligands or cell surface receptors, show the clear functions of sialic acids in negative regulation of cellular inflammation [32]. Thus, the high level of serum sialic acids recorded in dynamics among children with adhesion processes is related to desialized cell surfaces, thus proving that the inflammatory processes were more intense in fast acetylators compared to slow ones.

The level of protein-bound hydroxyproline (tHP) in our study was a truly intensifying collagen synthesis marker. Thus, fibrous tissue at hospitalization and on the first postoperative day was significantly higher in fast acetylator group compared to slow acetylators. However, this index decreased in both groups on the 3rd postoperative day onwards, showing its minimum values at discharge. Such a dynamics in tHP values can be explained by administration of early collagenolytic preventive treatment in rapid acetylators, a fact confirmed by recent studies [11].

The obtained results indicated an increase in ceruloplasmin and serum Cu level content in slow acetylators postoperatively, showing maximum values on the 5th postoperative day, then returning to normal range at time of discharge. The dynamics of fast acetylators indices was similar to that of slow acetylators, though they were no statistically relevant. As it is known, ceruloplasmin is an alpha 2 globulin that binds copper and is synthesized in hepatocytes. Ceruloplasmin is important for its biological functions in removing excessive catecholamines and serotonin via oxidation, as well as in inhibiting both serum histaminase and the oxidation of lipids in the cell membrane due to its anti-inflammatory and antioxidant action. Moreover, it has been found that macrophage-derived ceruloplasmin contributes significantly to protection against inflammation and tissue injury in acute and chronic experimental colitis [33]. The functional significance of ceruloplasmin, as well as a number of copper-containing enzymes, such as cytochromoxi-

dase, monoamine oxidase, tyrosinase, and superoxidismutase, were found to exert a strong antioxidant effect of annihilation on superoxide radicals, thus converting them into oxygen and water.

It can be concluded that the complex of specially selected biochemical examinations indirectly reflect the characteristics of collagen biosynthesis in children with different acetylation phenotypes, thus highlighting the role of acetylation in the development of intraperitoneal adhesion processes in children. The specifically rapid type of acetylation is characteristic for children with postoperative adhesive diseases. Adhesive intestinal obstruction more commonly occurred in fast acetylators compared to the group with slow acetylators. It has been proven that collagen synthesis was faster in fast acetylators associated with peritoneal inflammation, destructive appendicitis and due to surgical traumas, followed by a marked endotoxemia. Therefore, a major genetically determined adhesion process developed. It should be mentioned that adhesive intestinal obstructions in slow acetylators exhibited milder symptoms and lower levels of endotoxicosis, dehydration, and acid-base balance changes [34].

This study results are similar to data obtained by Golubeva M.N., who reported that children with fast acetylation phenotypes (greater than 76%) exhibited a higher rate of adhesion formation than lysis of adhesions in peritonitis [35]. The peritoneal injury in these patients leads to a marked intra-abdominal adhesion formation. However, slow acetylation phenotypes (less than 76%) showed a slower acetylation process. These children had poorly marked or absent intra-abdominal adhesion processes , following a severe or repeated peritoneal trauma. The study of Yakovleva O.A. et al. proved the importance of genotype and phenotype assessment of N-acetyltransferase as a predictor of bronchopulmonary diseases [36].

Acetylation is known to be crucial for metabolism. Acetylation is the ability of the body (genetically determined) to metabolize compounds that contain amino groups. Currently, there are more than 200 genes responsible for the metabolism of xenobiotics, defined as foreign substances that enter the body through different pathways, the N-acetyltransferase gene being one of them, which encodes the N-acetyltransferase. The enzyme activity might occur in the liver and different tissues, which further divides people into two groups, namely fast and slow acetylation phenotypes. The recent pharmacogenetic studies have established the heterogeneity of the human population in terms of the ability to metabolize drugs and other xenobiotics, which largely determines the efficacy and safety of the therapy performed.

The antiadhesion treatment was continued in outpatient care conditions due to some assessed biochemical parameter deviations, which persisted even at 20-25 days postoperatively.

The biopsy samples retrieved from different segments of the intraperitoneal cavity during surgery have provided important data for all stages of the evolutionary adhesion processes. The local and general reactive manifestations of the adhesive processes pose a significant threat on the growing body like in peritoneal hyperemia that is accompanied by the release of large amounts of biologically active substances into the blood flow. Furthermore, this leads to vascular stasis and a subsequent triggering of all mediating local inflammatory responses, which generally impair the overall condition, vital organs and proper system functioning. In turn, these different-origin aggressions are accompanied by functional impairment of the affected region. In this regard, further researches should be carried out to highlight the molecular mechanisms of intestinal fibrosis that would determine the main factors contributing to fibrotic process in general and particularly in intestinal fibrosis [37-39].

All the anatomical and pathological adhesion types were made up of a fibro-conjunctival axis with dilated capillaries. The adhesion processes lead to a pathological development of a major type of acute intestinal obstruction, mainly sited within the small bowel. Most of adhesions caused obstructions and repeated obstructions, which turned into an acute intestinal occlusion.

It can be concluded that the study group included complicated cases, from a clinical point of view, especially in patients, who required not only a complex and special diagnosis, but also a proper assessment of the biological field.

The assessment of homeostatic changes enabled confirming the crucial role of homeostasis rebalancing, by eradicating the pathological focus and resorption of necrotic tissues, as well as removing the excessive tissue proteolysis and exogenous substances, thus providing optimal regeneration conditions.

Therefore, the complex analysis of some pathophysiological mechanisms at different clinical and evolutionary stages in pediatric acute abdominal surgical pathology led to the development of a differentiated therapy, surgical approach + intensive pre-, intra- and postoperative therapy resulting in the most effective methods of treatment.

The obtained study results proved that the strictly individualized management of pre-, intra- and postoperative medical and surgical treatment allowed improving the previous poor prognosis, by reducing serious complications, as well as decreasing morbidity and mortality rate in acute intraperitoneal inflammatory surgical pathology.

The surgical treatment requires case-by-case individualized approach, taking into account the clinical, X-ray, ultrasound, and laboratory data, as well as the biohumoral features in terms of their severity and form. The beneficial effects of this treatment strategy are confirmed by a series of clinical studies [40-43].

It might be concluded that postoperative adhesions occur, following almost any abdominal surgery, whereas 20% of patients may have repeated episodes of adhesive obstructions, 80% of cases might experience possible relapses after appropriate conservative treatment, and 5% might report adhesive bowel obstructions, which do not improve symptoms even in using enemas or prokinetics , thus a relaparatomy is required. Prevention of adhesion formation requires early diagnosis, appropriate surgical treatment, and careful hemostasis in anastomosis, performed by using monofilament threads.

Further in-depth studies on the peculiarities of pediatric adhesion diseases are necessary in order to develop new strategies for prevention, diagnosis and effective, possibly differentiated and customized treatment.

Conclusions

1. The obtained study results were based on a group of 50 patients aged 1 month-18 years during 2011-2018 years, which showed that hospital morbidity rate, due to adhesive bowel obstruction, tends to steadily increase, whereas the clinical features, complications and challenges in diagnosis is still a medical and surgical topic of interest. This present study has completed the current data on the etiopathogenesis of intraperitoneal adhesion processes, thus confirming the crucial role of the microbial factor, inflammatory response mediators, cell and humoral immune activation, extension of the inflammatory process and the genetic factors due to the acetylation phenotype in children.

2. The dynamic methods of the research based on a series of modern, clinical, histological, biochemical, and bacteriological techniques allowed assessing the clinical and evolutionary disease stages, as well as the severity degree of its associated complications. The high level of postoperative inflammatory mediators indicated an exacerbation of the inflammatory process and tissue hypoxia, thus being a risk factor in the development of intraperitoneal adhesion processes and resulting in poor prognosis due to a recurrent acute intestinal obstruction. The comprehensive diagnostic methods used via modern paraclinical techniques allowed predicting their role in the development, evolution and prognosis of intraperitoneal adhesion process.

3. A conservative and differentiated treatment of abdominal intestinal obstruction in acute adhesion disease was used at first. The surgical treatment approach depended on the intraoperative condition, which allowed identifying the surgical techniques. However, all cases were likely to have a relapse of intestinal obstruction, especially in children with fast acetylation phenotype, therefore, a 2-4 year follow-up is required for patients who underwent surgery, via regular clinical, imaging, and laboratory investigations and antiadherent treatment (Serrata, Fermencol, Longidase, Collalysin + Wobenzym – anti-inflammatory, immunomodulatory drugs).

4. The scientific problem solved within this research refers to complementary data on clinical, paraclinical, and imaging peculiarities, as well as on the biochemical markers, particularly of N-acetyltransferase, which provided comprehensive information on the acetylation type, thus justifying the use of medical techniques.

5. In conclusion, further in-depth studies of this issue are required, particularly on the pathophysiology of collagen synthesis, the prophylaxis of the adhesion process and targeted antiadherent treatment. The use of Longidase, Fermenchol, Cuprinil and anti-inflammatory drugs over the last years has proved to reduce the inflammatory response, adhesion formation in patients operated on the abdominal cavity. Although 100% of patients who underwent surgery develop adhesion processes, the antiadherent treatment might substantially reduce the number of cases associated with acute intestinal obstruction, followed by surgical treatment. Therefore, a rational conservative treatment will reduce both the morbidity and mortality rates in acute adhesive intestinal obstructions.

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JB drafted the first manuscript, LB acquired and interpreted the data, VB interpreted the data, EG designed the trial and revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

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Conflict of Interests
The authors have no conflict of interests to declare.