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ABSTRACT

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COMPARATIVE CHARACTERISTICS OF CLINICAL AND LABORATORY MARKERS OF NUTRITION IN PREMATURE CHILDREN TAKING INTO ACCOUNT GESTATIONAL AGE AT BIRTH

Introduction. Current data from scientific literature indicate the need to create unified recommendations for diagnosing feeding intolerance in premature infants. It is known that clinical manifestations of digestive system dysfunction in the postnatal period are the cause of the subsequent development of persistent functional gastrointestinal disorders, which worsens the patients` quality of life. In general, recommendations for providing medical care to newborns with feeding intolerance in perinatal pathology are an important area of scientific research at the present stage.

Objective. To determine the main clinical and laboratory criteria for feeding intolerance in premature infants based on coprofiltrate parameters, considering gestational age and severity of the condition at birth.

Materials and Methods. A comparative analysis of clinical and laboratory criteria for feeding intolerance in perinatal pathology was conducted in premature children of different gestational ages. The list of laboratory parameters of coprofiltrate included: the levels of fecal calprotectin, albumin, α-1-antitrypsin, fecal elastase-1, and PMN-elastase.

Results. Clinical signs of feeding intolerance in premature infants include gastric residual volume > 50%, regurgitation and/or Banti syndrome, flatulence, blood in stools, acholic stools, and signs of endotoxemia. Laboratory markers of gastrointestinal disorders determined based on coprofiltrate studies are: increased levels of fecal calprotectin, albumin, α-1-antitrypsin, fecal elastase-1, and decreased PMN-elastase.

Conclusions. The results of our study suggest the primary role of the intestinal mucosa inflammation in the pathogenesis of neonatal feeding intolerance under conditions of hypoxia in perinatal pathology. It is

accompanied by decreased enzymatic activity, weakened local immunity, and increased intestinal mucosa permeability.

Keywords: infant, premature babies, gestational age, digestive system, feeding intolerance, gastrointestinal diseases.

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ПОРІВНЯЛЬНА ХАРАКТЕРИСТИКА КЛІНІКО-ЛАБОРАТОРНИХ МАРКЕРІВ ХАРЧОВОЇ НЕДОСТАТНОСТІ У ПЕРЕДЧАСНО НАРОДЖЕНИХ ДІТЕЙ З УРАХУВАННЯМ ГЕСТАЦІЙНОГО ВІКУ ПРИ НАРОДЖЕННІ

Вступ. Сучасні дані наукової літератури свідчать за необхідність створення єдиних рекомендацій для діагностики порушень харчової толерантності у передчасно народжених дітей. Відомо, що клінічні прояви дисфункції системи травлення у постнатальному періоді є причиною розвитку у подальшому стійких функціональних гастроінтестинальних розладів, погіршуючи якість життя пацієнтів. Узагальнення рекомендацій надання медичної допомоги новонародженим за наявності харчової інтолерантності при перинатальній патології є важливим напрямком наукових досліджень на етапі сьогодення.

Мета: Визначити основні клініко-лабораторні критерії харчової інтолерантності у передчасно народжених дітей на основі показників копрофільтрату з урахуванням гестаційного віку і тяжкості стану при народженні.

Матеріали і методи. Проведено порівняльний аналіз клініко-лабораторних критеріїв порушень харчової толерантності при перинатальній патології у передчасно народжених дітей різного гестаційного віку. Перелік лабораторних показників копрофільтрату включав: рівень фекального кальпротектину, альбуміну, α-1-антитрипсину, фекальної еластази-1 та PMN-еластази.

Результати. Клінічними ознаками порушень харчової толерантності у передчасно народжених дітей є наявність залишкового об'єму харчування > 50%, зригування та/або збільшені розміри печінки або гепатолієнальний синдром, метеоризм кишківника, домішки крові у випорожненнях, ахолічні випорожнення та ознаки ендотоксикозу. Лабораторними маркерами гастроінтестинальних порушень за дослідженнями показників копрофільтрату є: підвищення рівня фекального кальпротектину, альбуміну, α-1-антитрипсину, фекальної еластази – 1 та зниження показника PMN- еластази.

Висновки. Результати досліджень свідчать, що основним механізмом патогенезу при порушеннях харчової толерантності у новонароджених за умов гіпоксії при перинатальній патології є запалення слизової оболонки кишківника, що супроводжується зниженням місцевого імунітету, порушенням ферментативної активності та підвищенням проникливості слизової оболонки кишківника.

Ключові слова: немовля, недоношені діти, гестаційний вік, травна система, харчова непереносимість, шлунково-кишкові захворювання.

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INTRODUCTION

An important component of postnatal adaptation in newborns is the effective functioning of the gastrointestinal system (GIS) due to the need of the body to fully absorb the main food ingredients through enteral nutrition (EN). Insufficiency of the GIS functional state in premature infants (PMI) has a combined nature and is associated with the simultaneous dysfunction of several organ systems: the hepatobiliary system, pancreas, and intestine, which in turn correlates with gestational age at birth. Particularly severe and long-lasting disorders are observed in newborns with severe forms of perinatal pathology [1, 2]. A special role in this is played by the imperfection of the main regulatory systems, in particular the nervous, endocrine, immune, and antioxidant systems, which is inherent in the PMI organism under conditions of hypoxia and obstetric oxidative stress [3]. Strilchuk L. confirms the connection between immune deficiency and oxidative stress in PMIs [4].

Current data from scientific literature indicate the need to create unified recommendations for diagnosing feeding intolerance (FI) in this category of newborns, since they have a high risk of developing negative consequences in the future caused by hypoxic damage to the body, including, among others, the formation of GIS pathology. The frequency of FI in PMIs ranges from 33.80% to 53.45% [5, 6].

Providing full-fledged EN plays a decisive role in increasing survival rates and supporting health and quality of life, starting from the neonatal period. The criteria for FI in newborns and infants are actively discussed in modern scientific literature [2, 5, 6]. Today, there is no agreed-upon list of indicators based on proven sensitivity and specificity which could be recommended as generally accepted clinical and laboratory criteria. This justifies the feasibility of relevant scientific research to improve this therapeutic and diagnostic direction, considering the main pathogenetic links in the development of GIS disorders.

STUDY OBJECTIVE. To determine the main clinical and laboratory criteria for feeding intolerance in premature infants based on coprofiltrate parameters, taking into account gestational age and severity of the condition at birth.

MATERIALS AND METHODS

A comparative analysis of severe perinatal pathologies having clinical signs of functional GIS disorders was conducted in PMIs, taking into account the gestational age at birth. Group I consisted of 54 infants with a gestational age of 29–31/6 weeks, group II – 67 infants with a gestational age of 32–33/6 weeks, group III – 41 infants with a gestational age of 34–36/6 weeks; group IV – 50 apparently healthy infants with a gestational age of 34–36/6 weeks.

The correspondence between the morpho-functional maturity of infants and their gestational age at birth was determined using a complex of anthropometric parameters, the Ballard Maturational Assessment, and percentile tables. The inclusion criteria were: less than 37 weeks of gestation at birth, severe condition at birth, the need for primary resuscitation and intensive care, clinical forms of perinatal pathology with FI manifestations, signed informed consent of the infant's parents to participate in the study. Exclusion criteria were: gestational age of ≥ 37 weeks at birth, diagnosed congenital malformations, no signed informed parental consent.

The condition of newborns was assessed using the Apgar scale, and during follow-up, using the Score for Neonatal Acute Physiology with Perinatal Extension-II (SNAPPE II). The Neonatal Multiple Organ Dysfunction Score (NEOMOD, 2001) was used to diagnose multiple organ dysfunction syndrome (MODS) [7, 8, 9]. Nosological diagnoses were made according to ICD Classification, in particular, the following sections were used: Digestive system disorders of fetus and newborn (P75-P78); Feeding problems of newborn (P92). An analysis of the developmental histories of newborns was conducted (Form No. 097/o).

Clinical assessment of feeding intolerance was performed according to existing international recommendations, considering newborns' age [2, 10]. Matsyura O. supports the methodological basis of food allergy assessment, even in older children [11]. The list of laboratory parameters, in addition to traditional ones, included coprofiltrate parameters, in particular, the levels of albumin, α-1-antitrypsin (A1AT), fecal elastase-1 (FE-1), PMN-elastase, and fecal calprotectin (FC) were determined. The studies were carried out under agreement at the BUKINTERMED German-Ukrainian Laboratory (Chernivtsi, Ukraine) and the Cottbus Public Laboratory of Medicine, Microbiology and Infectious Epidemiology (Cottbus, Germany).

The studies were performed in compliance with the basic provisions of GCP (1996), the Council of Europe

Convention on Human Rights and Biomedicine (1997), the Declaration of Helsinki of the World Medical Association on the Ethical Principles for Medical Research Involving Human Participants (1964–2008), and the Order of the Ministry of Health of Ukraine No. 690 dated September 23, 2009 (as amended by the Order of the Ministry of Health of Ukraine No. 523 dated July 12, 2012). The study was approved by the Bioethics Committee of the Bukovinian State Medical University (Protocol No. 2 dated February 9, 2015).

Statistical processing of the study results was carried out using the Statistica software (StatSoft Inc., Version 13.0, USA). Statistical values were determined by considering standard deviation (S), standard error (m), and arithmetic mean (M); the Shapiro-Wilk criterion (normal distribution with the sample size of more than 30, $p<0.05$) and the Kolmogorov-Smirnov criterion were also used. The quantitative indicators in samples with a normal distribution were assessed using the Student's t-test; the statistical significance of the results was determined at $p<0.0001$. The diagnostic value of the used markers of EN disorders was determined by analyzing the Receiver Operating Characteristic Curve (ROC) with the calculation of the following indicators: cut-off level, area under the ROC curve (Area Under the curve of the Receiver Operating Characteristic, AUROC), 95% CI, and degree of confidence. The AUROC interval was classified into: 0.9–1 – excellent; 0.8–0.9 – very good; 0.7–0.8 – good; 0.6–0.7 – satisfactory; 0.5–0.6 – unsatisfactory. Analysis of the operating characteristics of diagnostic tests also included calculation of sensitivity (Sen) and specificity (Spe) indicators.

RESULTS AND DISCUSSION

Differences in sex and anthropometric characteristics in the comparison groups were as follows: among newborns from group I, there were 36 boys (66.67%) and 18 girls (33.33%), anthropometric characteristics at birth: weight 1105.66±128.53 g, body length 35.36±1.05 cm, head circumference 26.58±2.06 cm, chest circumference 24.86±2.04 cm; in group II – 50 boys (74.63%) and 17 girls (25.37%), birth weight 1548.82±141.47 cm, length 36.84±1.23 cm, head circumference 30.42±1.91 cm, chest circumference 27.91±2.06 cm; in group III – 61 boys (59.80%) and 41 girls (40.20%), birth weight 2278.49±210.02 cm, length 44.72±2.34 cm, head circumference 31.34±1.57 cm, chest circumference 30.24±1.52 cm; in group IV – 38 boys (62.30%) and 23 girls (37.70%), weight 2364.00±113.67 g, length 45.21±0.75 cm, head circumference 31.59±0.71 cm, chest circumference 30.51±1.46 cm. Infants of the comparison groups had a severe condition at birth, which was confirmed by the Apgar score: in group I – a score of 4.20±1.11 at the one-minute mark and 5.52±1.12 points at the five-minute mark; in group II – a score of 5.34±1.07 at the one-minute mark and 6.56±0.78 at the five-minute mark; in group III – a score of 5.43±0.27 at the one-minute mark and 6.58±0.33 at the five-minute mark, with indicators in group IV being 6.86±0.34 and 7.85±0.39, respectively.

The list of diseases detected in the PMIs of the comparison groups, taking into account the main and concomitant diagnoses, is presented in Table 1.

Analysis of the data provided in Table 1 showed that the list of clinical manifestations of maladaptation in PMIs was similar in all three groups, regardless of gestational age at birth; however, there was a slightly higher rate of pathology in newborns with a gestational age of 29–31/6 weeks. In particular, in group I, severe birth asphyxia was observed much more often, compared to other groups, accompanied by severe respiratory disorders, secondary to primary pulmonary atelectasis and hyaline membrane disease, with the development of multiple organ dysfunction syndrome (MODS), which, in addition to respiratory disorders, included changes in the central nervous system (in particular convulsive syndrome), cardiovascular system, gastrointestinal (GI) tract, as well as hemorrhagic manifestations and periventricular leukomalacia. In newborns of group II as compared to group III, a higher frequency of grade I subependymal hemorrhage was noted.

Signs of gastrointestinal system insufficiency were observed during examination in newborns of all comparison groups; the duration of gastrointestinal dysfunction depended to a certain extent on the course of perinatal pathology in general. Given the impossibility of PMIs to fully absorb the nutritional ingredients necessary for the existence of the body by the enteral route, all newborns were prescribed parenteral nutrition in the complex therapy.

An appropriate analysis was conducted in the comparison groups to study the features of the clinical manifestations of neonatal FI with regard to the gestational age at birth. The results obtained are presented in Table 2.

The analysis results showed that the rate of clinical signs characterizing the presence of FI in PMIs tends to increase in correlation with the decrease in the gestational age of newborns according to all criteria. A significant difference in indicators between the comparison groups was found for Banti syndrome and clinical signs of endotoxemia. Scientific publications of recent years indicate that signs of FI in PMIs are usually manifested by increased gastric residual volume (GRV) > 50% of the previous feed volume, vomiting and/or abdominal distension, as well as blood in the stool [12, 13].

Table 1 – Clinical pathology in newborns in the comparison groups

Parameter	Group I (n, %)	Group IIA (n, %)	Group IIIA (n, %)
Severe asphyxia	32 (59.26) *#	13 (19.40)	23 (22.55)
Moderate asphyxia	22 (40.74)	23 (34.33)	20 (19.61)
Respiratory disorders:			
severe	54 (100) *#	29 (43.28)	41 (40.20)
moderate	-	27 (40.30)	27 (26,47)
mild	-	11 (16.42)	34 (33.33)
Primary pulmonary atelectasis	50 (92.59) *	23 (34.38)	-
Congenital pneumonia	4 (7.41)	7 (10.45)	-
Hyaline membrane disease	38 (70.37) *	24 (35.82)	-
Morpho-functional immaturity	18 (33.33) #	11 (16.42)	7 (6.86)
Small for gestational age	19 (35.19)	13 (19.40)	14 (13.73)
Cerebral coma	8 (14.81) *	3 (4.48)	-
Cerebral edema	8 (14.81)	5 (7.46)	14 (13.73)
Intraventricular hemorrhage grade 1	8 (14.81)	9 (13.43)	14 (13.73)
Intraventricular hemorrhage grade 2	9 (16.67) #	7 (10.45)	4 (3.92)
Intraventricular hemorrhage grade 3-4	4 (7.41)	3 (4.48)	-
Subependymal hemorrhage grade 1	-	24 (35.82)	7 (6.86)
Subependymal hemorrhage grade 2	-	13 (19.40)	14 (13.73)
Periventricular leukomalacia	9 (16.67) #	8 (11.94)	4 (3.92)
Non-specific ulcerative enterocolitis grade 1	11 (20.37)	5 (7.46)	-
Non-specific ulcerative enterocolitis grade 2	4 (7.41)	-	-
Multiple organ dysfunction syndrome involving:			
central nervous system	54 (100) *#	29 (43.36)	14 (13.73)
cardiovascular system	16 (29.63) *	3 (9.37)	15 (14.71)
respiratory system	30 (100.00) *	9 (28.12)	27 (26.47)
gastrointestinal system	54 (100.00)	67 (100.00)	102 (100.00)
hemorrhagic syndrome	17 (31.48)	1 (3.12)	7 (6.86)
anemia syndrome	15 (27.78) *	1 (3.12)	7 (6.86)
convulsive syndrome	17 (31.48) #	11 (16.42)	14 (13.73)
DIC syndrome	14 (25.93) #	4 (12.48)	7 (6.86)

Notes (with regard to the Bonferroni correction):

** – a statistically significant difference between the indicators of groups I and II, p<0.02;*

 # – a statistically significant difference between the indicators of groups I and III, p<0.02;

+ – a statistically significant difference between the indicators of groups II and III, p<0.02

Table 2 – Comparative characteristics of clinical manifestations of feeding intolerance in newborns of different gestational age at birth

Parameter	Group I (n, %)	Group II (n, %)	Group III (n, %)
Feeding intolerance (gastric residual volume > 50%)	54 (100.00)	67 (100.00)	102 (100.00)
Regurgitation/vomiting	32 (59.26)	46 (68.66)	64 (62.74)
Enlarged liver	54 (100.00)	67 (100.00)	102 (100.00)
Banti syndrome	43 (79.63) *#	35 (52.24)	39 (38.24)
Intestinal flatulence	48 (88.89)	49 (73.13)	62 (60.78)
Blood in stools	28 (51.85) #	29 (43.28)	34 (33.33)
Acholic stool	8 (14.81)	7 (10.45)	7 (6.86)
Endotoxemia	45 (83.33) #	48 (71.64)	54 (52.94)

Notes (with regard to the Bonferroni correction):
** – a statistically significant difference between the indicators of groups I and II, p<0.02;*
 # – a statistically significant difference between the indicators of groups I and III, p<0.02;
+ – a statistically significant difference between the indicators of groups II and III, p<0.02

Some laboratory markers were analyzed in this work in order to determine possible laboratory parameters that may be used as additional criteria for FI diagnosis and to explain the pathophysiological mechanisms of FI development. These indicators included the levels of FE-1, A1AT, PMN-elastase, albumin, and FC in the coprofiltrate of newborns. The results obtained are presented in Table 3.

Table 3 – Comparative characteristics of coprofiltrate biomarkers in the newborns of comparison groups (M±m)

Parameter	Group I (n=54)	Group II (n=67)	Group III (n=102)	Group IV (n=50)
Fecal calprotectin (FC), µg/g	392.47±19.63~*#	409.46±19.31~+	185.43±9.27~	64.74±3.11
Albumin, µg/g	39.24±2.94~	40.26±3.01~+	38.92±1.95~	11.28±0.90
α1-antitrypsin (A1AT), µg/g	89.32±4.49~*	384.25±19.21~+	478.44±25.77~	241.15±18.90
PMN-elastase, ng/g	289.58±14.49~*#	90.45±5.04~+	189.72±9.49~	257.53±17.30
Fecal elastase-1 (FE-1), µg/g	358.42±2.89 ~*#	270.68±18.04 ~	267.63±13.38~	246.98±16.79

Notes (with regard to the Bonferroni correction):
~ – a statistically significant difference between study groups and the controls, p<0.01;
** – a statistically significant difference between the indicators of groups I and II, p<0.01;*
 # – a statistically significant difference between the indicators of groups I and III, p<0.01;
+ – a statistically significant difference between the indicators of groups II and III, p<0.01

The obtained average levels of coprofiltrate indicators showed significant differences with regard to the gestational age of newborns in the comparison groups. The level of FC, which indicates intestinal mucosal inflammation, tended to increase more significantly in newborns of group II vs. the controls – up to 409.46±19.31 µg/g, while there was a significant decrease in group I – up to 392.47±19.63 µg/g. According to the literature data, the increase in FC levels is due to its release from activated neutrophils. An increase in this parameter confirms the transepithelial migration of granulocytes into the intestinal lumen, which indicates the inflammatory nature of the disease [14, 15, 16]. Increased intestinal mucosa permeability due to local inflammation causes protein loss in the body, which is confirmed by an increased albumin level in the coprofiltrate of newborns in all comparison groups. It should be remembered that increased intestinal mucosa permeability can also lead to a possible reverse translocation of pathogenic and opportunistic microflora and endotoxins to the bloodstream, which increases the risk of developing infectious inflammation. The A1AT parameter was significantly decreased in newborns of groups I, II, and III vs. the controls. At the same time, we observed the tendency towards a lower level in correlation with decreasing gestational age – 478.44±25.77, 384.25±19.21, and 89.32±4.49 µg/g, respectively. According to the literature data, A1AT is considered an antiprotease that is able to neutralize excess proteases, inhibit chemotaxis and adhesion of neutrophils.

Research results confirm the growing role of pro-inflammatory and anti-inflammatory biomarkers in the clinical differentiation of pathologies of various etiology, particularly in the gastrointestinal tract [17].

Synthesis of A1AT occurs in the endoplasmic reticulum of the liver, polymorphonuclear neutrophils, alveolar macrophages, as well as monocytes, enterocytes, and Paneth cells. It is able to inhibit the production of pro-inflammatory cytokines and regulate reactive oxygen species, respectively activating the body's anti-inflammatory response [18, 19, 20]. Analysis of the results also showed a decrease in the level of PMN-elastase, which is secreted from granulocytes and has a regulatory effect on the body's inflammatory and immune responses. The decrease in this parameter also indicates insufficient regulation of anti-inflammatory mechanisms of the intestinal mucosa in PMIs. A significant increase in the level of PMN-elastase in newborns of group I was noteworthy, which, in conditions of profound organism immaturity, may be associated, in our opinion, with the inadequacy of stress mechanisms associated with hypoxic damage.

In newborns of the main study groups, an increased level of FE-1 was also noted. Increased level of FE-1 as compared to the controls may be the result of the body's stress response due to hypoxic inflammation, which requires attention, since it may be one of the manifestations of subclinical pancreatic disorders in PMIs, which is confirmed by literature data [21, 22, 23]. A significant increase in FE-1 level in extremely premature infants is of particular note.

Taking into account the characteristic differences in infant coprofiltrate parameters and their role in the pathophysiological mechanisms of FI development in perinatal pathology, ROC analysis was performed to determine sensitivity and specificity. The results obtained are presented in Table 4.

Table 4 – Coprofiltrate ROC curve analysis in the newborns of comparison groups

Parameter	AUC	Standard error	p	95 % CI	Sen, %	Spe, %
FC, µg/g	0.977	0.0216	<0.0001	0.930–0.996	98.55 92.2–100.0	97.83 88.5–99.9
Albumin, µg/g	0.859	0.0391	<0.0001	0.781–0.917	80.60 69.1–89.2	97.83 88.5–99.9
A1AT, µg/g	0.841	0.0392	<0.0001	0.761–0.903	71.64 59.3–82.0	84.78 71.1–93.7
FE-1, µg/g	0.538	0.0568	0.5010	0.439–0.635	52.24 39.7–64.6	77.50 61.5–89.2
PMN-elastase, ng/g	0.805	0.0482	<0.0001	0.720–0.874	83.58 72.5–91.5	89.13 76.4–96.4

According to the results of ROC analysis, the most significant parameters were FC, albumin, PMN-elastase, and A1AT with regard to sensitivity and specificity.

Thus, based on the analysis of ROC curves and their operating characteristics of coprofiltrate indicators, the following laboratory criteria can be recommended along with clinical manifestations for confirming feeding intolerance in PMIs with severe perinatal pathology:

- increased FC level at a threshold value > 390.15 µg/g (AUC 0.977; 95% CI 0.930–0.996; p < 0.0001; Sen 98.55%, 95% CI 92.2–100.0; Spe 97.83%, 95% CI 88.5–99.9);
- increased albumin level at a threshold value > 37.25 µg/µl (AUC 0.859; 95% CI 0.781–0.917; p < 0.0001; Sen 80.60%, 95% CI 69.1–89.2; Spe 97.83%, 95% CI 88.5–99.9);
- increased A1AT level at a threshold value > 452.67 µg/g (AUC 0.841; 95% CI 0.761–0.903; p < 0.0001; Sen 71.64%, 95% CI 59.3–82.0; Spe 84.78%, 71.1–93.7);
- decreased PMN-elastase level at a threshold value < 95.49 ng/g (AUC 0.805; 95% CI 0.720–0.874, p < 0.0001; Sen 83.58%, 95% CI 72.5–91.5; Spe 89.13%, 95% CI 76.4–96.4).

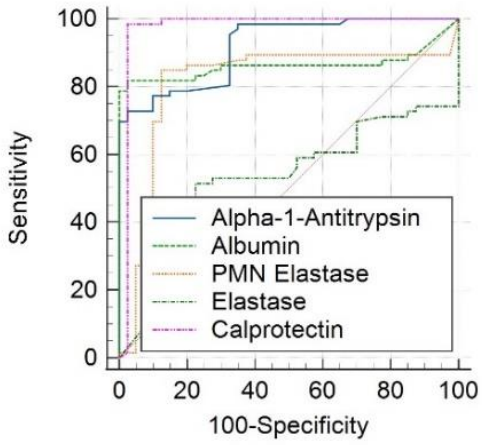

Diagram 1 – Analysis of ROC curves of coprofiltrate parameters in PMIs of comparison groups

Thus, based on the conducted studies, it can be concluded that feeding intolerance in PMIs with severe perinatal pathology can develop based on hypoxic inflammation of the intestinal mucosa. This hypoxic inflammation causes a local immunity disorder, a decrease in enzymatic activity, and an increase in the permeability of the mucosa and leads to a risk of opportunistic and pathogenic microflora entering the systemic circulation, which aggravates the manifestations of endotoxicosis and increases the risk of developing a septic process. Innovative biotechnological approaches, particularly experimental models using cell cultures, open up new opportunities for studying inflammation and metabolism of the intestinal mucosa [24]. The use of additional laboratory diagnostic methods based on coprofiltrate indicators is useful for confirming the diagnosis of FI in PMIs, and allows us to clarify the main pathophysiological mechanisms of FI development for the purpose of timely, well-founded treatment.

CONCLUSIONS

1. Clinical signs of feeding intolerance in premature infants include gastric residual volume (GRV) > 50%, regurgitation and/or Banti syndrome, flatulence, blood in stools, acholic stools, and signs of endotoxemia.
2. Laboratory markers of gastrointestinal disorders determined based on coprofiltrate studies are: increased levels of fecal calprotectin, albumin, α-1-antitrypsin, fecal elastase-1, and decreased PMN-elastase.
3. Analysis of studies indicates the role of intestinal mucosa inflammation in the pathogenesis of feeding intolerance, which is accompanied by decreased enzymatic activity, weakened local immunity, and increased intestinal mucosa permeability.

PROSPECTS FOR FUTURE RESEARCH

Prospects for further research include a multifactorial correlation analysis of clinical and laboratory indicators that characterize the development of FI in PMIs, in order to prepare appropriate recommendations for practical healthcare use.

AUTHOR CONTRIBUTIONS

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2. Drafting the work or reviewing it critically for important intellectual content.
3. Final approval of the version to be published.
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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