

# The role of carbohydrate malabsorption syndrome in the pathogenesis of rotavirus diarrhea (a literature review)

O. V. Usachova<sup>1</sup>, N. V. Vorobiova<sup>1</sup>, E. A. Silina<sup>2</sup>, T. B. Matvieieva<sup>2</sup>

<sup>1</sup>Zaporizhzhia State Medical and Pharmaceutical University, Ukraine, <sup>2</sup>CNE "Zaporizhzhia Regional Clinical Hospital of Infectious Diseases" of the Zaporizhzhia Regional Council, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

**The aim** – to summarize literature data on the pathogenetic mechanisms of the diarrheal syndrome development in children with rotavirus infection and to determine the role of carbohydrate malabsorption syndrome in it through a complex analysis of literature reviews and empirical studies.

Rotavirus infection (RVI) remains the main cause of severe dehydrating gastroenteritis in children under five years of age. One of the most important pathogenetic links of rotavirus gastroenteritis is the development of osmotic diarrhea induced by carbohydrate malabsorption syndrome. Its development is associated with disaccharidase insufficiency and impaired absorption of monosaccharides in the small intestine.

Carbohydrate malabsorption syndrome is found in 67.0–98.3 % of children with RVI. Its laboratory manifestations (an increase in levels of fecal carbohydrates and lactose) are observed starting from the first days of the disease, and the maximum indicators are recorded in the period from the fifth to the seventh day.

**Conclusions.** Carbohydrate malabsorption syndrome is observed in the absolute majority of children with RVI, and its maximum severity is noted from the fifth to the seventh day of the disease, being realized mainly due to lactase deficiency. The severity of carbohydrate malabsorption syndrome can be influenced by concomitant pathological conditions, that lead to a decrease in the activity of disaccharidases in the small intestine, and the metabolic activity of the intestinal microbiota.

## Keywords:

rotavirus infection, pathogenesis, diarrhea, carbohydrate malabsorption syndrome, lactase deficiency, children.

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\*E-mail: kdibzdmu@gmail.com

## Місце синдрому мальабсорбції вуглеводів у патогенезі ротавірусної діареї (огляд літератури)

O. V. Usachova, N. V. Vorobiova, E. A. Silina, T. B. Matvieieva

**Мета роботи** – узагальнити відомості щодо патогенетичних механізмів розвитку діарейного синдрому при ротавірусній інфекції у дітей та визначити роль у ньому синдрому мальабсорбції вуглеводів шляхом комплексного аналізу оглядів фахової літератури й емпіричних досліджень.

Ротавірусна інфекція (РВІ) залишається основною причиною тяжких дегідратуючих гастроентеритів у дітей віком до п'яти років. Одна з найважливіших патогенетичних ланок ротавірусного гастроентериту – розвиток осмотичної діареї, що спричинена синдромом мальабсорбції вуглеводів. Його розвиток пов'язаний із дицукридазною недостатністю та порушенням абсорбції моноцукридів у тонкому кишечнику. Синдром мальабсорбції вуглеводів виявляють у 67,0–98,3 % дітей із РВІ. Його лабораторні прояви (підвищення рівня вуглеводів і лактози у фекаліях) визначають, починаючи з перших днів хвороби, а максимальні показники фіксують у період від п'ятої до сьомої доби.

**Висновки.** Синдром мальабсорбції вуглеводів визначають в абсолютній більшості дітей із РВІ, він досягає максимальної виразності з п'ятої до сьомої доби хвороби та реалізується передусім шляхом лактазної недостатності. На виразність синдрому мальабсорбції вуглеводів можуть впливати супутні патологічні стани, що призводять до зниження активності дицукридаз у тонкому кишечнику, та метаболічна активність кишкової мікробіоти.

## Ключові слова:

ротавірусна інфекція, патогенез, діарея, синдром мальабсорбції вуглеводів, лактазна недостатність, діти.

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Rotavirus infection (RVI) remains the leading cause of severe gastroenteritis with dehydration in young children, despite the global introduction of vaccination. It accounts for more than 200,000 deaths annually [1,2,3]. Rotavirus is the most common cause of acute gastroenteritis in children in all European countries. In Western Europe, the incidence of RVI ranges from 1.33 to 4.96 cases per 100 individuals each year, and the number of patients hospitalized for rotavirus gastroenteritis varies in different countries from 7 % to 81 % [4,5]. In different regions of Ukraine, its share is from 34.0 % to 63.1 % among all cases of hospitalized children due to acute intestinal infections [6,7].

The high prevalence of RVI among the pediatric population, the significant incidence of complicated disease

courses, and the high level of child mortality associated with this infection, actualize RVI as an urgent problem of pediatric infectious diseases and necessitate further studies on its pathogenetic features.

One of the most important pathogenetic aspects of RVI is carbohydrate malabsorption syndrome, which is observed in 63–98% of children from the first days of the disease [8,9,10].

## Aim

To summarize literature data on the pathogenetic mechanisms of the diarrheal syndrome development in children with rotavirus infection and to determine the role of carbo-

hydrate malabsorption syndrome in it through a complex analysis of literature reviews and empirical studies.

**Modern ideas about pathogenetic mechanisms of rotavirus gastroenteritis. Carbohydrate malabsorption syndrome.**

The pathogenesis of RVI is complex and multicomponent. Rotavirus infects mature non-proliferating enterocytes of the upper and middle parts of the villi and enteroendocrine cells of the proximal small intestine and causes diarrhea as a result of damage to highly differentiated enterocytes involved in membrane digestion (leading to malabsorption). Extracellular NSP4 (eNSP4) – the secretory form of NSP4, released from rotavirus-infected cells, binds to neighboring uninfected intestinal villi and crypt cells, increases the concentration of  $Ca^{2+}$  in the cytoplasm through a phospholipase C-dependent calcium signaling pathway that activates calcium-dependent chloride channels. Activation of these channels leads to an excessive secretion of  $Cl^-$  into the intestinal lumen, generating an osmotic gradient that facilitates the water transport into the lumen, implementing the main secretory mechanism of rotavirus-induced diarrhea [11, 12, 13].

The second important mechanism of secretory diarrhea in RVI is activation of the intestinal nervous system [3, 14]. NSP4 stimulates intestinal enterochromaffin cells to release 5-hydroxytryptophan (5-HT), which activates 5-HT<sub>3</sub> receptors on afferent nerves of the intermuscular plexus. This causes an increase in intestinal motility and activates the neurons of the submucosal nerve plexus to release vasoactive intestinal peptide from the nerve endings located next to the crypt cells, in which the level of cAMP increases and, as a result, the secretion of NaCl and water into the intestinal lumen is stimulated [3, 12, 15].

In addition, rotaviruses cause disruption of tight junctions between enterocytes with an increase in paracellular permeability and increased water outflow from the intercellular space to the intestinal lumen due to a decrease in the expression of tight junction-related proteins such as ZO-1 and occludin in infected cells [16, 17].

The scientist views on the pathogenetic links of carbohydrate malabsorption syndrome in RVI are still mixed. Thus, some literary sources report about the absence of noticeable morphological signs of damage to the small intestinal epithelium during acute respiratory viral infection in the presence of only pronounced functional disturbances of enterocytes [18, 19]. However, the majority of modern scientific works testify to rotavirus-associated alterations in the intestinal mucosa, such as shortening and atrophy of villi, loss of microvilli, distention of the endoplasmic reticulum, mitochondrial swelling in enterocytes, nuclear vacuolization, pyknosis and lysis of mature enterocytes as well as detachment of villi [12, 20, 21].

Scientists have now demonstrated that rotavirus causes cell death of infected enterocytes, activating the internal caspase-dependent pathway of apoptosis in them due to expression of the proapoptotic protein Bax stimulated by NSP4 enterotoxin [22]. Also, NSP4 induces the caspase 3-dependent pathway of apoptosis associated with the mitochondrial membrane depolarization and the cytochrome C release into the cytosol [23]. In addition, at the late stages of infection, rotavirus NSP1 protein initiates p53-dependent pro-apoptotic signaling through diminishing the NSP1-p53 interaction and pro-apoptotic protein p53 stabilization [12]. In an experimental study by Ye Zhao et al., it has been shown

that in rotavirus-infected IPEC-J2 cells, apoptotic changes were observed in 34.2 % of cells after 24 hours [24].

Some rotavirus isolates are even currently being studied as oncolytic agents due to their ability to induce apoptosis of affected cells [25, 26]. In addition to apoptosis, rotavirus and its enterotoxin NSP4 cause enterocyte death by necroptosis through the activation of the RIPK1 / RIPK3 / MLKL necroptosis pathway [22]. The rate of death of mature functionally active enterocytes located at the tips of the villi exceeds the growth rate of immature enterocytes regenerating from the stem cells at crypts [11, 22]. Thus, L. Paparo et al. have demonstrated the slowing of proliferative processes in the human intestinal Caco-2 cells under the influence of rotavirus and shown that almost 70 % of infected cells were arrested in G0/G1 phase of the cell cycle, unlike uninfected cells that were in G2 phase [16]. Thus, rotavirus infection causes a decrease in the epithelial surface area and replacement of mature functionally active enterocytes, which provide membrane digestion through the synthesis of disaccharide enzymes and absorption of monosaccharides, by immature (cryptic) cells, which leads to the syndrome of carbohydrate malabsorption.

Digestion and absorption of oligo- and disaccharides occurs in the small intestine mediated by glycosyl hydrolases located in the cytosol and on the small intestinal brush border membrane. They cleave di- and oligosaccharides into monosaccharides (glucose, galactose, fructose), which are then absorbed and transported inside the cell by the main co-transporter of  $Na^+$ -D-glucose SGLT1 and facilitative glucose transporters GLUT2 and GLUT5 [18, 27]. The main intestinal glycosyl hydrolases are lactase-phlorizin hydrolase (LPH), sucrase-isomaltase (SI), maltase-glucoamylase (MGA), trehalase (TREH) [28, 29, 30].

Rotavirus has been proven to cause a decreased expression of enterocyte-specific genes – LPH (lactase-phlorizin-hydrolase), SGLT1 and L-FABP in infected cells at mRNA and protein levels starting 6 hours after infection [21]. Rotavirus enterotoxin NSP4-induced suppression of the intestinal brush border enzyme LPH expression results in the development of secondary lactase deficiency, and a decrease in the activity of SGLT1 on villus enterocyte membranes leads to a disruption of the  $Na^+ -D$ -glucose symport, which ensures the reabsorption of large volumes of water in physiological conditions [28, 31, 32].

Enterocyte-specific gene knockdown together with apoptotic loss of mature enterocytes and their replacement by less differentiated, dividing cells, results in defective absorptive function of the intestinal epithelium and disaccharide deficiency. Undigested carbohydrates with high osmotic activity accumulate in the small intestinal lumen and contribute to further extravasation of tissue fluid into the intestinal cavity, which is the basis of the osmotic diarrheal component in RVI [5, 33]. In the lower parts of the small and large intestine, the intestinal microflora metabolizes undigested oligosaccharides with the formation of gases such as  $H_2$ ,  $CO_2$ ,  $CH_4$  and short-chain fatty acids (SCFA), the intestinal contents shift to acidic pH, which leads to a significant increase in peristalsis [34].

Carbohydrate malabsorption syndrome, as one of the main pathogenetic mechanisms of rotavirus diarrhea, is realized to a greater extent in young children, since milk and dairy products form the basis of their diet, and lactose

makes up 80–85 % of milk oligosaccharides, being the main carbohydrate and source of energy at this age [10,34].

The development of carbohydrate malabsorption syndrome in children with RVI is reported in a number of modern scientific studies [8,9,35]. According to Y. Hu et al., lactose malabsorption in the debut of rotavirus gastroenteritis was noted in 67 % of cases and was observed significantly more often than in diarrhea of non-rotavirus origin [8]. In the dynamics of RVI, this syndrome develops in the absolute majority (98.3 %) of young children [9].

Studies on the total level of undigested carbohydrates in children of the first two years of life with RVI have reported an increase in it already in the first days of the disease [8,9,36]. Ivanko O. H., Bondarenko V. M. set this indicator at the level of 0.5 [0.4; 0.5] % [36]. A study conducted on the dynamics of rotavirus gastroenteritis has found that the maximum laboratory manifestations of carbohydrate malabsorption syndrome were observed in the later stages of the disease – from the fifth to the seventh day, which was confirmed by the highest levels of fecal carbohydrates – 0.75 [0.50; 1.65] % and 0.87 [0.40; 1.65] %, respectively, without normalization of the indicators on the tenth day [9].

Data from experimental studies on an increase in the total content of undigested carbohydrates and lactose in children from the early days of rotavirus gastroenteritis are confirmed by the described mechanisms of osmotic rotavirus diarrhea [3,31,37]. An experimental study has demonstrated that in rotavirus-infected NSP4-positive enterocytes, the expression of lactase and SGLT1 genes was significantly reduced 6 hours after infection, amounting to only 15–22 % of control levels. A significant decrease in SGLT1 mRNA levels was observed up to the seventh day, lactase-phlorizin hydrolase – up to the tenth day of the infection, which is entirely in accordance with the data on the duration of oligosaccharide digestion disorders in children with RVI [21].

A study to assess clinical and laboratory manifestations of carbohydrate malabsorption syndrome in young children with RVI has shown an association between oligosaccharide metabolism violations in the small intestine and lactase deficiency, as evidenced by a strong direct correlation between total fecal levels of carbohydrates and lactose at all stages of the disease ( $r = 0.91$ ;  $r = 0.86$ ;  $r = 0.91$ ;  $r = 0.89$ , on the 3<sup>rd</sup>, 5<sup>th</sup>, 7<sup>th</sup> and 10<sup>th</sup> days, respectively) [9]. Moreover, the most severe syndrome of carbohydrate malabsorption due to lactase deficiency was seen in children of the first six months of life with maximum fecal levels of reduced carbohydrates and lactose exceeding the indicators in children of the second six months of life by 1.2 times and 2.7 times, respectively [9]. The important role of lactase deficiency in the pathogenesis of rotavirus gastroenteritis is also evidenced by modern literature data on the effectiveness of adding exogenous lactase to the RVI therapy in children resulting in stabilization of the frequency of bowel movements, regression of flatulence phenomena, normalization of the undigested carbohydrate content and fecal acidity occurred twice as fast [38]. The predominance of lactase deficiency in malabsorption syndrome in RVI children can be explained by the apical location of the small intestinal brush border enzymes on the enterocyte microvilli [30], the absence of cross-fermentation in contrast to other disaccharides, such as

sucrase-isomaltase and glucoamylase [28,30], as well as a greater dominance of lactose over other carbohydrates in the diet among young breastfed children.

**Factors influencing carbohydrate malabsorption syndrome in rotavirus infected children.** It has now been proven that the clinical manifestations of carbohydrate malabsorption syndrome and secondary lactase deficiency in children can vary depending on the combined effect of a number of factors: the level of lactase-phlorizin-hydrolase enzymatic activity, the amount of lactose ingested, the individual intestinal sensitivity, the intestinal microflora state, etc. [10,39].

The lactose breakdown in the human body and other mammals is provided by the only enzyme – lactase-phlorizin hydrolase (LPH). The enzyme is an integral protein containing two enzymatic activities:  $\beta$ -D-galactoside hydrolase, which hydrolyzes lactose to glucose and galactose, and glycosyl-N-acetyl-sphingosine-glucohydrolase, which provides hydrolysis of phlorizin [40,41]. LPH is synthesized as a monomeric pro-LPH molecule with four domains (I–IV). During transport to the apical membrane, the precursor peptide is subjected to a series of O- and N-glycosylation, domains I and II are removed, whereupon the active enzyme is formed – a 150-kDa protein consisting of domains III and IV, which are responsible for phlorizin hydrolase and lactase activity, respectively. In this way, the mature enzyme is transported to the enterocyte brush border membrane [40,42].

In humans, LPH is expressed only in the small intestine and is restricted to absorptive villus enterocytes [43]. The distribution of the enzyme along the villus-crypt axis is uneven. The crypt zone cells move towards the villus tip, simultaneously undergoing the process of differentiation. The high activity of lactase, as well as other disaccharidases (sucrases, isomaltases), is provided precisely by mature differentiated enterocytes located at the top of the villi. The largest amount of  $\beta$ -glycosidase complex (lactase) is localized on the apical enterocyte surface [44]. This arrangement explains the more frequent occurrence of lactase deficiency (compared to other enzyme deficiencies) with damage to the small intestinal mucosal membrane. The maximum level of the enzyme catalytic activity is observed in the proximal parts of the jejunum and gradually decreases in the direction to the ileum [41].

From the study by R. C. Reed it is known that among all disaccharides, the lactase enzyme activity is most often reduced in inflammatory process in the intestinal mucosa. Thus, isolated lactase deficiency was observed in 27.2 % of cases, while all 4 enzymes were deficiently active in only 9.5 % of cases, and in only 1.3 % of cases – deficiency of other disaccharides with normal activity of lactase was noted [45].

Acute gastroenteritis of predominantly viral etiology, including RVI in the top spot, is believed to be the main cause of the secondary disaccharide insufficiency development in children [8]. However, violation of the breakdown and absorption of carbohydrates in the intestine can develop in other pathological conditions which result in damage to enterocytes amid inflammatory, atrophic, immune processes in the intestine. In the presence of such morphological signs of inflammation in biopsies of the duodenal mucous membrane as reduction and atrophy of villi, lymphocytic and

eosinophilic infiltration of the lamina propria, a decreased activity of disaccharides (lactases, maltases, sucrases) was observed in 78.2 % of cases [45].

Among the main causes of secondary disaccharide insufficiency are irritable bowel syndrome, nonspecific ulcerative colitis, Crohn's disease, celiac disease, Whipple's disease, resection of the small intestine, long-term use of cytostatics, antibiotics, parenteral nutrition [27,30].

It is known that lactase deficiency is registered with a high frequency in patients with giardiasis [46]. It has been experimentally proven that the parasite eradication in a person infected with *G. duodenalis* led to the regression of the malabsorption syndrome clinical manifestations and the restoration of the villar microstructure in the small intestine [47]. According to the literature, immune damage to the structure of enterocytes and their destruction is accompanied by allergic inflammation of the intestinal mucosa causing carbohydrate malabsorption [48].

Today, it has been proven that osmotic diarrhea developed only when the amount of oligosaccharides entering the colon exceeded the fermentation capacity of the microflora *in situ* [10].

It is known that the number of bacteria in the upper intestine varies in a narrow range –  $10^3$ – $10^4$  CFU/ml of intestinal contents, while in the lower parts it reaches  $10^{12}$ – $10^{14}$  CFU/ml [49]. All representatives of the lower gastrointestinal tract microflora are obligate and facultative anaerobes, energy production for which is associated with incomplete oxidation of organic compounds (fermentation). Colonic bacteria metabolize carbohydrates and proteins to short-chain fatty acids (SCFA), mainly acetate, propionate, butyrate and gases:  $H_2$ ,  $CO_2$ ,  $CH_4$  [50,51]. Next, carbon dioxide is mostly converted into acetate, hydrogen is absorbed and excreted through the lungs, and organic acids are utilized by microorganisms. During fermentation, a number of intermediate metabolites are also produced, such as lactate, ethanol, and succinate, which later become the basis to synthesize dietary fiber [52,53].

Sucrolytic intestinal microbiota has high metabolic activity. For example, only *Bacteroides thetaiotaomicron* contains 260 glycoside hydrolases in its genome [54]. Fermentation of 50–60 g of carbohydrates per day produces 500–600 mmol of dietary fiber in the intestine [55]. He T. et al. have shown in their study that 80.6 % of cultured fecal bacteria synthesized the enzyme  $\beta$ -galactosidase (hydrolyzed lactose to galactose and glucose, which were further metabolized to SCFA and  $H_2$ ,  $CO_2$ ,  $CH_4$ ), indicating its high activity in the colon [56]. Among the entire range of intestinal microflora, the main producer of  $\beta$ -galactosidase is *Bacteroides / Prevotella*, accounting for 70 % of the total  $\beta$ -galactosidase activity of the intestinal microflora. In addition, *Bifidobacterium*, *Eubacterium rectal*, *Clostridium coccoides*, *Atopobium*, *Streptococcus*, *Lactococcus*, *Lactobacillus*, *Enterococcus*, *Peptostreptococcus* and *Ruminococcus* have shown  $\beta$ -galactosidase activity in the experiment [56,57]. Another study has revealed that genes encoding  $\beta$ -galactosidases were relatively numerous in the genus *Bacteroidetes* [58]. It has also been proven that among lactose-fermenting bacteria, the activity of  $\beta$ -galactosidase can change up to 4 times [56].

Thus, the number and composition of bacteria with  $\beta$ -galactosidase activity is an important factor influencing

lactose metabolism in the colon and can determine the severity of malabsorption syndrome.

In the case of a decreased disaccharide activity of the enterocyte brush border, the osmotic load of unfermented lactose and other oligosaccharides in the small intestine causes water and electrolyte transport from plasma to the intestine resulting in osmotic diarrhea. However, the microflora reacts to disaccharide insufficiency by hyperreactivating various bacterial groups which can completely metabolize excess simple carbohydrates to SCFA and gases, which is an important mechanism for reducing osmotic load [59,60].

It is known that the long-term use of lactose reduces the severity of lactose malabsorption symptoms in maldigesters, which may be associated not only with a decrease in the symptom perception by subjects and adaptive changes in the colon (transit, motility), but also with adaptive changes in the colonic microbiota by increasing the activity of fecal  $\beta$ -galactosidase. When incubated with lactose *in vitro*, it has been noted that the fecal bacteria in lactose maldigesters produced a greater amount of lactate, acetate, propionate and butyrate and at a faster rate than the fecal microflora in lactose-tolerant individuals, which might also be associated with adaptive changes in the intestinal microflora to conditions of higher disaccharide concentration [39].

The results of modern studies using simulation models of the large intestine during lactose loading have indicated an increase in the relative number of *Actinobacteria* (at the expense of *Bifidobacterium*) and *Firmicutes* (at the expense of *Lactobacillus*) with  $\beta$ -galactosidase activity, and inhibition of the proteobacteria growth, which are incapable of fermentation lactose, as well as an increase in the concentration of intestinal metabolites (lactate, acetate, propionate, and butyrate) [61,62].

The probability of the lactose colonic fermentation influence on the development of osmotic diarrhea depends on the balance between the ability of the intestinal microbiota to ferment disaccharides and the colonic capacity to remove fermentation metabolites [39]. During the conversion of lactose into SCFA by intestinal bacteria, the osmotic load increases 8-fold. However, it is believed that SCFA are quickly absorbed through the mucous membrane of the large intestine [39,52]. Low capacity of the intestinal microflora, which leads to inefficient removal of undigested lactose or its intermediate metabolites (glucose, galactose) or low colonic absorptive capacity, which causes inefficient removal of terminal metabolites (SCFA), can induce osmotic diarrhea [39]. This has been confirmed by the study results of scientists from China, demonstrating that it was high concentrations of lactose, lactate and galactose, but not SCFA, that led to hyperosmosis in the large intestine lumen [63].

According to T. He et al., if the colon can absorb SCFA at a sufficient rate, the higher enzymatic capacity of the colon microbiota for lactose can reduce the intensity of its malabsorption [39].

## Conclusions

1. One of the most important pathogenetic mechanisms of RVI, especially in children of the first years of life, whose diet is based on milk and dairy products, is carbohydrate malabsorption syndrome, which occurs due to the development of disaccharidase (mainly lactase) deficiency and

impaired monosaccharide absorption in the small intestine caused by the rotavirus NSP4 protein action resulting in osmotic diarrhea.

2. Laboratory signs of carbohydrate malabsorption syndrome are observed in 67.0–98.3 % of children with rotavirus infection and reach their maximum expression from the fifth to the seventh day of illness without normalization of indicators during early convalescence in most of them. This syndrome is realized mainly due to lactase deficiency in young children.

3. The severity of carbohydrate malabsorption syndrome and secondary lactase deficiency, particularly in children with rotavirus infection, can be affected by concomitant pathological conditions which lead to a decrease in the activity of disaccharides in the small intestine, as well as the intestinal microbiota metabolic activity.

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#### Information about the authors:

Usachova O. V., MD, PhD, DSc, Professor, Head of the Department of Pediatric Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.

ORCID ID: 0000-0003-0250-1223

Vorobiova N. V., MD, PhD, Assistant of the Department of Pediatric Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.

ORCID ID: 0000-0001-7610-8067

Silina E. A., MD, PhD, Assistant of the Department of Pediatric Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.

ORCID ID: 0000-0002-3199-9297

Matvieieva T. B., MD, Head of the Department No. 4, Communal Non-Profit Enterprise "Zaporizhzhia Regional Clinical Hospital of Infectious Diseases" of Zaporizhzhia Regional Council, Ukraine.

ORCID ID: 0000-0003-1195-0151

#### Відомості про авторів:

Усачова О. В., д-р мед. наук, професор, зав. каф. дитячих інфекційних хвороб, Запорізький державний медико-фармацевтичний університет, Україна.

Воробіова Н. В., PhD, асистент каф. дитячих інфекційних хвороб, Запорізький державний медико-фармацевтичний університет, Україна.

Сіліна Є. А., канд. мед. наук, асистент каф. дитячих інфекційних хвороб, Запорізький державний медико-фармацевтичний університет, Україна.

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