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ROTAVIRUS INFECTION IN NEWBORNS CHILDREN: CLINICAL PERFORMANCE, TREATMENT AND PROPHYLAXY

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GENERAL CHARACTERISITCS

Theme relevance. Recently role of rotavirus (RV) in infectious pathology of infants and young children has significantly increased. According to WHO, frequency of rotavirus infection (RVI) in neonates and infants ranges from 11% to 71% (WHO, ARJ, 2002).

Such RV properties as unique genome structure, genetic plasticity, low contamination dose, high contagiousness and resistance to most disinfectants cause high risk of nosocomial infection in children with inpatient treatment (Dzyublik I.V. et al., 2003; Frantzidou F. 1997, Rynichi O., 1998).

Today rotovirus is the most common cause of nosocomial infection in newborns and premature infants in intensive care units, neonatal pathology, nursing preterm obstetric hospitals and children's hospitals (Vasilyev B.J. et al. 2000; O'Ryan M. et al. 1996). RV circulation in the hospital is a prognostic marker for outbreak of nosocomial infection in infants and is a complex medical problem (Kirin V.M., Katonina S.P., 1999; Chang E.J. et al. 2002).

High level of morbidity, severe clinical forms causing development of bacterial and viral-bacterial complications, nosocomial outbreaks, and high risk of disability among infants recovering from a disease generalized form contribute to high relevance of RVI in infants (Anisimova J.N. et al., 1993; Gajardo R. et al., 1997).

RVI nosocomial outbreaks in infants are characterized by severe clinical course, with rapid development of exsicosis, metabolic disorders, and possible development of toxic infectious shock and high mortality (Yashida A. et al., 1995; Makino M. et al., 1996; Foldenauer A. et al., 1998).

In the recent years the problem of microbiological health of newborns is of particular relevance. It is during peri- and neonatal period that immunological mechanisms of adaptation and protection of the child are formed, being the basis for physiological growth and development of the child in the first years of life (Berezhnaya V.V. et al., 2000, Tutchenko L.I. et al., 2001; Kramareva S. et al., 2001).

According to modern conceptions, RV causes physiological disorder of body microbiocenosis of the newborns in maternity hospitals, disorder of natural immunological defense against bacteria strains, viruses and fungi that colonize a newborn with severe perinatal pathology during intensive therapy (Yatsik A.V., Zakharova N.I., 1997; Bochkov I.A. et al., 1998). On this background there may be severe RVI clinical forms with the development of viral and bacterial complications (sepsis, pneumonia, acute haematogenous osteomyelitis, meningitis, encephalitis) that are often fatal (Shun'ko E.E. 1995; Kramareva S. et al. 2001).

However, RV is one the least studied pathogens in infants.

The complexity of RVI issue is caused by lack of rapid methods of diagnosis and screening for rotavirus in pregnant women and newborns in maternity wards, intensive care and neonatal intensive care, neonatal pathology departments and nursing preterm infants children's hospitals (Shunko E.E. et al., 1998 ; Vasilyev B.J. et al., 2000). There is a lack of statistical data on RV risk factors for neonates in these hospitals. Almost no data are present regarding RV impact on postnatal adaptation and progress in perinatal pathology of newborns, clinical course of disease in term and preterm infants. No effective prevention of RVI has been developed in these institutions, which would take into account the clinical and epidemiological features of RVI in infants, provided formation of peri- and neonatal physiological intestinal biocenosis in the newborn.

A promising direction in the treatment of RVI is use of recombinant interferon drugs (IFN) and enterosorbents. However, do far there are no effective methods and schedules of use for these drugs in the treatment of infants.

Therefore, further research problems in newborns with RVI to address these issues is extremely important and is one of the promising reserves to reduce infant morbidity and mortality.

Aim of the study. To improve the efficiency of clinical diagnosis, treatment and prevention of RVI in newborns by implementing complex preventive measures based on clinical and virological studies and identifying RVI risk factors.

In accordance with the intended aim, **research tasks** were:
1. To study incidence and dynamics of RV diagnosis in newborns in obstetric hospitals, pathology departments and neonatal nursing centers for preterm infants.
2. To study peculiarities of early neonatal period in infants infected with RV.
3. To study the clinical course of RVI in term and preterm infants.
4. Determine the leading risk factors in newborns with RVI in obstetric hospitals and accidence of nosocomial infection in newborns with various forms of perinatal pathology in the departments of nursing for infants and premature babies.
5. To develop clinical and virological monitoring and prevention of RVI in newborns.
6. To improve methods for comprehensive treatment of RVI in newborns using alpha-2b-interferon (Laferon) and Enterosgel.

Study object - rotavirus infection in infants.
Study subject - clinical course of RVI in newborns, its diagnosis, treatment and prevention.
Research methods - general clinical, virologic, serologic, microbiological, statistical method.

Practical significance of the results.
Within practical healthcare RVI monitoring has been recommended in newborns with perinatal pathology for early diagnosis and prevention of nosocomial RVI, based on clinical, virological and microbiological monitoring ("Monitoring RVI in newborns with perinatal pathology" - Information Letter No. 71- 2002 from 15/01/02).
Clinical and epidemiological features of RVI have been stablished, expecially of clinical diseases in infants depending on gestational age, RVI leading risk factors in infants and express diagnostic methods. Mathematical regression models have been developed to predict the frequency of RVI depending on the timing of inpatient stay, laboratory diagnostics algorithm RVI in newbrns, clinical and diagnostic RVI criteria in infants and effective preventive measures. The materials were included in the guidelines ("Laboratory diagnosis of rotavirus infection" - Kyiv, 2002.) and ("Rotavirus infection: clinical manifestations, diagnosis and comprehensive treatment" - Kyiv, 2003.).
An integrated approach to the treatment of infants with RVI has been approved, including use of Laferon, Enterosgel and correction of microecological disorders using multiprobiotic Symbiter. Use of drug Laferon has been introduced in the practice of pathology departments and neonatal nursing institutions for preterm infants ("Use of Laferon in the treatment of neonatal RVI" - Information Letter No. 13-2004.

Publications. The thesis materials include 15 publications: four articles, four collections of scientific papers, three conference theses collections; two newsletters, two guidelines and eight articles have been published in the journals that are on the list, approved by HAC of Ukraine.

Work structure and volume. The thesis is a computer text typed in 158 pages, consists of an introduction, 6 chapters of the research, analysis and synthesis of results, conclusions, practical recommendations and a list of references. The work is illustrated with 29 tables and 28 figures. List of refrences includes 262 names (140 Ukrainian and 122 works of CIS and foreign authors) and contains 26 pages.

Materials and methods. Thesis materials included clinical and virological laboratory tests in the hospitals for newborns and neonatal intensive care units, as well as children's hospitals for neonatal pathology and premature babies, Kyiv, in 1996-2001.
Study methods were based on generally accepted methods of determining basic biochemical parameters, bilirubin and fractions by Iendrassik method (1938), ALT and AST levels by Reitman-Frankel method (1962), total and protein fractions by electrophoresis on biuret paper, urea, blood glucose , K +, Na + serum C-reactive protein. CBC and urinalysis were conducted as well.
Levels of serum immunoglobulin G, M, A were determined by Manchini radial immunodiffusion (1968).
Antigen values (AG) of influenza viruses, parainfluenza, adenovirus, RS virus were assessed in nasopharyngeal washings and rectal washout by immunofluorescence using specific sera.
Coxsackie viruses A, B in the feces were determined by ELISA, AG of these viruses in the rectal washout – by immunofluorescence method.
Bifidobacteria titre in the feces was determined at feces culture on Blaurock or thioglycollate medium with microscopy. Presence of over 2-3 opportunistic pathogen bacteria strains was considered pathological colonization, which was more than 10^5-10^6 colony forming units (CFU) and bifidobacteria titer at 10^4-10^7. In case of abnormal colonization with OPB, biological properties were defined, including adhesiveness, hemolityc properties and resistance to antibiotics.
Specific laboratory diagnosis of RVI was performed determining RV AG with rotavirus diagnostics "Rotatest." RV AG titer 1: 16-1: 32was considered diagnostic, a study was conducted for admission of the child to the department om the first 3-5 days and over every 7-10 days. As a reference method, ELISA test with "Rotapast" system, in some cases - directly or immune electron microscopy (TEM, IEM) was used. Specific antyrotavirus serum antibodies were determined using RHNH. The titer 1:16 was considered diagnostic, with the titer increasing over time by 2-4 times. The study materials included feces and blood serum.
Due to the winter-spring seasonal rise in RVI incidence, the research conducted from December to March.
Statistical analysis of the results was performed using the methods of variation statistics with computer expert medical analysis program Statistics, version 5. As Gaussian distribution model was used, we applied parametric method for assessing the differences of two samples for secondary Student criterion (t); arithmetic mean (M), standard error (m) and the distance of differences between some figures in the groups (p) was calculated. Stochastic dependence and the relationship between the individual parameters was determined by the correlation coefficient. Using software packages and mathematical processing of statistical regression model, the relationship was determined between the individual indicators.
Taking into account aims and tasks of the research, a comprehensive clinical and virological laboratory examination and analysis of perinatal risk factors was conducted in 201 newborns from birth to one month.
In the first phase clinical and virological examination was conducted, with analysis of perinatal risk factors in 43 newborns born at gestation term of 38-40 weeks in physiological department of the hospital and separated from their mothers.
Frequency and dynamics of RV in infants was studied depending on the length of their hospital stay.
To determine the leading risk factors for RV infection of newborns, maternal obstetrical history, especially during pregnancy and childbirth, postnatal adaptation of the newborns was analyzed. The influence of rotavirus on the course of early neonatal period in newborns was also studied. Clinical observations included assessment of gestational age, birth status of children with Apgar scale, and indicators of physical development, with record of symptoms in the course of postnatal adaptation. Recorded clinical indicators of postnatal adaptation in newborns included dates first breastfeeding, body mass dynamics, time of reduction of umbilical cord stump, stool

character, changes in skin color, turgor of tissues, physiological activity reflexes, status of physical activity and muscle tone, rectal temperature and body temperature.
At the second stage the complex clinical and laboratory examination included 43 preterm and 115 full-term infants with perinatal pathology, who were admitted from maternity hospitals or specialized departments of neonatology with clinical manifestations of hypoxic or hypoxic-hemorrhagic CNS lesions, hyperbilirubinemia, respiratory distress syndrome, gastrointestinal disorders, fetal infections etc. Due to RV reproduction only in mature differentiated enterocytes, a group of premature infants inclided children with gestational age of 32-36 weeks. The average gestational age was 35.1 ± 0.2 weeks.
In this group of infants the frequency and dynamics of RV diagnosis was studied depending on the length of stay in neonatology department. Leading RV risk factors in newborns with perinatal pathology were determined. The features of early postnatal adaptation were analyzed for newborns in which RV AG was detected, with the RVI symptoms when transferred to specialized neonatal department. Clinical course of RVI was studied in 27 full-term and 77 preterm infants with perinatal pathology.
A fact drew attention on analyzing the data of laboratory studies, that along with RV, opportunistic pathogenic bacteria or their combination were identified in preterm infants at a concentration of 10^6 in 1 g of feces and more in 14 (51.9%) full-term and 59 (76.6%) preterm babies: *E.coli*, *Proteus sp*., *Citrobacter sp.*, *Klebsiella pneumoniae*, *E. aerogenes*, *Pseudomonas aeruginosa*, *St. epidermidis*, *St. aureus*.
In 7 (25.9%) full-term and 25 (32.5%) preterm infants AG of respiratory viruses were detected along with opportunistic pathogenic bacteria: influenza, parainfluenza, adenovirus, RS-virus.
In these infants main clinical symptoms of mono-RVI RVI and mixed RV were compared in association with opportunistic pathogenic bacteria and respiratory viruses.
At the next stage, RVI monitoring and preventive measures were developed for early diagnosis and prevention of nosocomial RV infection in these hospitals based on the data of clinical and virological studies and leading risk factors for infection of newborns in terms of the hospital pathology departments and nursing departments for full-term and premature babies.
In complex RVI therapy in newborns methods were developed and tested using recombinant α-2b-IFN – Laferon and Enterosgel.
Laferon was used in the treatment of 27 patients in saline enemas, 50-10,000 IU / kg 2 times a day for 3-5 days. At the same time, vitamins C and E were prescribed orally, 30-50 mg / kg per day. Enterosgel was used in the treatment of 25 patients orally with normal saline, 5 g / kg 3 times a day for 5 days. To correct RVI microbiocenosis and treat all children in the study group, multyprobiotic Symbiter was administered, 0.5 oral doses twice a day for 10 days. In all children basic therapy was conducted.
The results were compared with those of control group (20 children) who received only basic therapy. Children in all groups were matched for gestational age, birth weight, weight status, and level of influence of the most important perinatal risk factors.
Efeiciency criteria of therapeutic measures: regression of clinical symptoms, laboratory parameters (coprological RV studies), decrease of complications incidence, duration of antibiotic therapy and hospital stay.

Results and discussion. Nosocomial RV infection was diagnosed in newborns of physiological hospital departments. According to the results of virological examination of 43 newborns in the hospital, born at gestation term of 38-40 weeks and separated from their mothers, in 19 (44.2%) infants RV and AG were found. In 5 (11.6%) infants RV AG detected in the first days of life in diagnostic titers of 1:16 to 1:64, confirming the possibility of RV infection newborns during birth or in the first hours of life (Blokhyna T.A. et al., 1991; Semyna A.N. et al., 1992). In 11 (25.6%) infants RV AG dynamics was found in the first 3 days of life in diagnostic titers of 1:16 to 1: 128, in 8 (18.6%) - RV between days 4-7 of the two-week stay in the Neonatology department of the hospital, which was regarded as nosocomial RV.

The results of virological research on RV frequency in the stool of newborns is closely related to the period of their inpatient stay, as evidenced by definite correlation coefficient r = 0.89. The maximum RV frequency is marked on 1-3 days of life of newborns seoarated from their mothers, as shown in the graph (Figure 1), when formation of primary biocenosis takes place.

Among perinatal risk factors for infection of newborns in the hospital the most important were likely: obstetric interventions during delivery (C-section) ($p < 0.05$); intranatal acute hypoxia ($p < 0.05$) - these children were first breastfed after day 1 of life ($p < 0.01$).

Apgar scores on the minutes 1 and 5 of life of newborns with RV AG in feces was significantly lower ($p < 0.05$, $p < 0.05$), causing the need of intensive care, which increased the risk of infection.

Newborns with defined RV AG, were first breastfed after an average of 28.8 ± 5.9 hours after birth, vs 8.9 ± 1.4 hours in the comparison group ($p < 0.01$), indicating a significant impact of this factor on incidence of RV AG. Thus, in thecase of first breastfeeding by 28.8 ± 5.9 h, the frequency of RV AG was 100%. Thus, it is proved that a late start of beastfeeding increases the RVI risk in newborns. The data confirm the fact that in the absence of "skin to skin" contact in the colostric feeding period or physiological breastfeeding, which can be provided by a common stay with the mother, a newborn receives no parent lacto- and bifidobacteria and secretory immunoglobulin A, essential for physiological formation of primary biocenosis (Tutchenko L.I. et al., 2001; Berezhnaya V.V. et al., 2003; Shunko E.E. et al., 2003) and protection against RV contamination.

Length of inpatient stay of babies with RV AG was on the average 7.5 ± 0.6 days vs 5.75 ± 0.2 days in the comparison group ($p < 0.01$), confirming the existing correlation between the frequency of nosocomial infection and length of inpatient stay.

Thus, it was found that the late first breastffeding reduced colonization resistance of the body of the newborn and the length of inpatient stay over 5 days was likely to increase RVI risk factors in newborns at the hospital.

Newborns with AG RV in feces had a greater weight loss (205.7 ± 16 g) compared with children without RV AG (157.1 ± 13 g, $p < 0.05$). Hyperbilirubinemia was observed more frequently (36.8% vs. 8.3%) and longer, increasing the content of indirect bilirubin levels in newborns of the study group (236 ± 29.5 mmol / l), while in the comparison group it did not significantly exceed the norms ($p < 0.05$).

At the second phase the frequency and dynamics of RV diagnosis was studied in 43 full-term and 115 preterm infants with perinatal pathology depending on the term of stay in the Neonatology department and leading RVI risk factors in these infants.

In carrying out virological studies it was found that in 9 (20.9%) full-term and 22 (19.1%) preterm infants RV AG were identified in feces in the diagnostic titers on admission to the department. During treatment and nursing babies in the hospital neonatology department incidence of RV AG was noted, as evidenced by a 3.1 times increase in the frequency of RV diagnosis in full-term infants and 3.9 times in preterm infants. After 2-3 weeks of hospitalization frequency of RV AG diagnosis in full-term infants was 28 (65.1%), preterm - 85 (73.9%). It was established that the maximum frequency of RV diagnosis in full-term infants was noted in the second week, in the preterm infants - at the end of the first month of stay in the Neonatology department.

The frequency of RV diagnosis in feces of the surveyed children is closely related to their inpatient stay, proving defined correlation coefficient r = 0.96 for full-term and r = 0.95 for premature infants (Figure 2).

Using software packages on mathematical processing of statistical regression model, correlation was identified between the indicators: $y = - 0.0912 x^3 + x^2 + 0.954 + 0.9013x + 28.505$ - for full-term and $y = 50.103 x^{0.344}$ - for preterm infants, where Y - the percentage of children with Rv diagnosis, X - stay in the hospital.

Thus, the results of virological monitoring have revealed nosocomial RV spread among infants in the neonatal department of pathology and nursing of preterm infants.

During December-March 2000-2001, the frequency of RV AG diagnosis was studied in feces of sick newborns and premature infants staying together with their mothers. It was established that the incidence of RV AG diagnosis in feces was 33.7%. It is statistically proven that a separated stay of a mother with a newborn significantly increases the frequency of RV AG diagnosis.
Essential RVI risk factors were established in term and preterm infants with perinatal pathology in terms of neonatology department. The leading factor in full-term newborns were: complicated pregnancy (89.3%, $p < 0.05$), urogenital infections (35.7%, $p < 0.01$), preeclampsia, III degree (39.3%, $p < 0.05$), SARS in the last trimester of pregnancy (28.6%, $p < 0.05$); intrapartum factors: premature amniorrhea (50.0%, $p < 0.01$), cesarean section (21.4%, $p < 0.05$), intranatal acute hypoxia (39.3%, $p < 0.05$).
Among RVI perinatal risk factors in preterm infants obstetrical history (43.5%, $p < 0.01$) is of importance, as well as miscarriage, medical abortion; complicated pregnancy (71.8%, $p < 0.05$), urogenital infections (30.6%, $p < 0.01$), preeclampsia, III degree (24.7%, $p < 0.01$), SARS in the last trimester of pregnancy (23.5%, $p < 0.01$); intrapartum premature amniorrhea (48.2%, $p < 0.05$). That is, on the background of chronic intrauterine fetal hypoxia and asphyxia of newborns, acute and chronic urogenital infections and extragenital disorders, microbiological health disorder occurs in the fetus and newborn with the development of RVI.
Early postnatal adaptation disorders were observed in all full-term newborns with RV AG in feces (40 (93%) and preterm 85 (100%) infants. Among postnatal risk factors in children birth in a state of asphyxia ($p < 0.05$) and the use of invasive resuscitation measures ($p < 0.01$) had probable value tracheal intubation, as well as prolonged ventilation in 3 (10.7%) full-term ($p < 0.05$) and in 15 (17.7%) preterm ($p < 0.01$) infants, major vessels catheterization - 9 (32 1%) full-term ($p < 0.01$) and in 22 (25.9%) preterm ($p < 0.05$) newborns, infusion therapy in 20 (46.5%) full-term ($p < 0.05$) and 72 (84.7%) preterm ($p < 0.05$), antibiotic therapy in 20 (46.5%) full-term ($p < 0.01$) and in 59 (69.4%) preterm infants ($p < 0, 05$), tube ffeding in 4 (14.3%) full-term ($p < 0.01$) and in 48 (56.5%) preterm infants ($p < 0.01$). Due to significant disorders of early neonatal period 23 (53.5%) full-term and 85 (100%) preterm infants were fed with pasteurized milk or formula.
Thus, the absence of physiological intrapartum colonization in fetus and newborn, unfavorable course of perinatal period lead to abuse of microecological adaptation in newborns, resulting in formation and development of perinatal pathology and colonization of the gastrointestinal tract with opportunistic bacteria and RV, contributing to the development of nosocomial RVI.
RVI was diagnosed in newborns, which had clinical signs of hypoxic-ischemic CNS lesions in the early neonatal period (71.4%, 90.6%, respectively in full-term and preterm infants), respiratory distress (21.4%, 76.5%), conjugation hyperbilirubinemia (42.9%, 48.2%), gastrointestinal disorders (39.3%, 24.7%), intrauterine malnutrition-III (57.1%, 58.8%) and edema syndrome (21.4%, 29.4%), hepatosplenomegaly (14.3%, 8.2%), anemia (14.3%, 10, 6%). Clinical RVI manifestations were observed in 27 (62.8%) full-term and in 77 (67%) preterm infants with perinatal pathology, in which virological studies had diagnosed RV AG.
It has been established that RVI in newborns with perinatal pathology was characterized by considerable severity - 62.9% severe and 37% moderate forms in full-term infants, 62.3% and 37,7% in preterm infants, respectively. Mild forms of the disease were not present. Disease onset was acute in 77.8% of full-term and 61% of preterm infants. The remaining patients experienced gradual development of infection for 2-3 days.
In 96.3% of full-term and 98.7% in preterm infants early clinical RVI signs matched with symptoms of general intoxication: deterioration in general condition during treatment of perinatal pathology, depression, reduced muscle tone and physiological reflexes, weakness or akertness, sluggish sucking, food refusal. Typical features of intoxication syndrome included hemodynamic disturbances in the form of pallor, mottled skin, cyanosis of the skin, observed in 22 (81.5%) full-term and 50 (64.9%) preterm infants. In 7 (25.9%) full-term and in 21 (27.3%) preterm patients with clinical signs of intoxication and exsicosis cardiac disorders were observed: tachycardia, muffled heart tones, expanded borders of relative heart dullness, systolic

murmur; sometimes the size liver increased, accompanied mostly by deep hemodynamic disturbances. Fever was observed in 9 (33.3%) full-term and 18 (23.4%) preterm infants.
The second frequency symptom was diarrhea, which was observed in 22 (81.5%) full-term and in 57 (74%) with oreterm patients. Stool was rare, watery, yellow or yellow-green. Frequency of defecation was 4-10 times a day in moderate form, with severe form - 7-15 times a day. RV AG titer in the feces of these children was 1:16 - 1:64, with an increase up to 1: 620 - 1: 1024 in some children. Prolonged diarrhea was on average 11-12 days. Viruses were found in the feces on the first day of clinical symptoms during an average of 16 ± 1.3 days. In 3 patients rotavirus was diagnosed on days 30-36, and in one patient on day 56, being dangerous in epidemic respect.
In 16 (59.3%) full-term and in 52 (67.5%) preterm patients with RVI gastrointestinal disorders were marked: vomiting with milk, sometimes mixed with bile (44.4%, 61% - in full-term and preterm, respectively), enteral indigestion (37%, 20.8%), abdominal bloating (66.7%, 63.6%). Dehydration, garde III was observed in 37% full-term and 42.9% preterm infants.
RV etiologic role was confirmed in the development of ulcerative-necrotic enterocolitis (UNE) in newborns. Thus, in 8 (29.6%) full-term and in 24 (31.2%) preterm infants RVI performance was accompanied by the UNE. The status of infants was severe, with pronounced manifestations of intoxication, acute abdominal bloating, vomiting with milk, then with milk mixed with bile, pallor, mottled skin, dehydration II-III grade, and liquid green excrement mixed with mucus. RV AG titer in the feces of these children was 1: 32-1: 64, with an increase up to 1: 160-1: 1024 in some infants.
Respiratory manifestations were observed in 14 (51.9%) full-term and in 43 (55.8%) preterm infants as breathing disorders, difficulty breathing through the nose, mucous excretion from the nose, upper respiratory tract, cough, lung wheezes.
In 32 (41.6%) preterm infants RVI course was accompanied by emergence or intensification of respiratory distress syndrome, tachypnea, intercostal retraction, and nasal flaring during breathing.
Thus leading RVI symptoms in newborns have been established: intoxication with hemodynamic disorders, watery diarrhea, vomiting, bloating, enteral indigestion, dehydration, grade III., respiratory manifestations.
No probable differences regarding the frequency and characteristics of clinical course of main RVI symptoms depending on gestational age were found.
In addition, RVI course in newborns with perinatal pathology occurred on the background of various pathological conditions, namely hyperbilirubinemia, respiratory distress, preiintraventricular hemorrhage (PIVH), hemorrhagic syndrome, seizures, thrombocytopenia, anemia, on the background of IgG in 55.6% of full-term (3.87 ± 0.3 g/l) and 74% of perterm infants (4.53 ± 0.14 g/l).
It has been found that in infants with perinatal pathology in conditions of neonatology departments combined rotavirus and bacterial, rotavirus and viral infection prevailed with more severe clinical condition in babies.
In 14 (51.8%) full-term and in 59 (76.6%) preterm infants in the study of intestinal microflora opportunistic bacteria or their combinations was defined in concentrations of 10^6 in 1 g of feces or more (Figure 3).
In 7 (25.9%) full-term and in 25 (32.5%) preterm infants mono-RVI (10.7%; 12.9% - in full-term and preterm infants, respectively), parainfluenza (14.3%; 22.4%), adenovirus (3.6%; 4.7%), RS virus (3.6%; 2.4%) was detected in the flushing of the bowels along with opportunistic bacteria.
The clinical course of mixed RVI was significantly more severe compared to mono-RVI course due to greater frequency and duration of diarrhea ($p < 0.05$), vomiting ($p < 0.01$), enteral indigestion ($p < 0.01$), catarrhal symptoms ($p < 0.05$) and more severe temperature reaction ($p < 0.01$).
Based on identified leading risk factors for RVI in infants, analysis of clinical symptoms and results of virological studies, clinical diagnostic criteria for neonatal RVI have been developed (Fig. 4).

RVI in infants should be considered as a risk factor for the development of septic diseases. According to the results of our research, nosocomial viral and bacterial complications were diagnosed in 14 (51.9%) full-term and in 36 (46.8%) preterm children with RVI: sepsis (22.2% and 20.8%, respectively) acute hematogenous osteomyelitis (18.5%, 9.1%), meningitis, encephalitis (3.7%, 5.2%), pneumonia (11.1%, 18.2%). That is, the data confirm the fact that intestinal colonization with RV and opportunistic bacteria increases the risk of "translocation" of viruses and bacteria with clinical manifestations of generalized viral and bacterial infections.

It was established that use of Laferon in RVI treatment improves clinical effectiveness of the treatment, namely intoxication duration decreases by 1.8 times, gastrointestinal disorders – by 1.5 times, diarrhea - by 1.4 times, respiratory disorders – by 1.8 times, hyperbilirubinemia - by 1.6 times, duration of antibiotic treatment was reduced by 1.6 times, sepsis - by 1.9 times, inoytient stay - by 1.6 times. Administration of Laferon reduces the frequency of septicopyemic foci in infants with mixed RVI by 2.6 times. Incidence of HAI was reduced 1.7 times, pneumonia – by 2.5 times, sepsis was reduced twice. RV duration was reduced by 1.6 times.

It has been found that in infants receiving Enterosgel, RV AG content in the feces decreased by an average of 72.0 ± 0.3%, by the end of the day 2, by 87.0 ± 0.4 % at the end of the day 3, while on day 4 RV AG was not found out at all in the feces of sick children. Use of Enterosgel in RVI treatment has reduced the duration of intoxication and gastrointestinal disorders by 1.5 times, diarrhea – by 1.4 times, hyperbilirubinemia – by 1.6 times, duration of antibiotic therapy - by 1.6 times, which helped to shorten inpatient stay by 1.4 times.
Prevention of RVI in newborns is based on providing microecological aspect of reproductive health and microbiological health of the fetus and newborn.

Preventive measures in the hospital:
1. Providing physiological formation of primary biocenosis.
a). Early breastfeeding of the child;
b). "Skin to skin" contact of a mother and a child;
c). Colostric feeding period;
g). Joint stay of mothers and infants with breastfeeding.

2. Minimal period of inpatient stay.
3. Conducting clinical, virological and microbiological monitoring.
Preventive measures in a specialized neonatology department:
1. Ensure formation of physiological intestinal biocenosis:
a). Breastfeeding;
b). The joint stay of mother and child at all stages of neonatal care.
2. Application of multiprobiotics to correct microecological violations.
3. Limitation of invasive interventions during intensive care.
4. Rational antibiotic therapy.
5. Reducing length of inpatient stay.
6. Conducting clinical, virological and microbiological monitoring in the ICU or neonatal pathology department.

CONCLUSIONS

In the thesis, theoretical results of clinical and virological RVI research in newborns have been generalized. Methods of complex treatment of RVI in infants have been improved, clinical diagnostic criteria and preventive measures against RVI in newborns have been developed based on the analysis of results of clinical and virological studies and major risk factors.

1. Accidence of RV in neonatal physiology department at the inpatient stay with separation of mothers and infants is 44.2%. Accidence of RV in newborns with perinatal pathology in the department of pathology of premature infants and nursing children's hospitals with separation of mothers and children is 65.1% in full-term children, 73.9% in preterm children, 33.5% in common inpatient stay of mothers and children. Moreover, RV accidence correlates with the length of inpatient stay.
2. Negative impact of RV on the course of early postnatal adaptation has been established. Disorder of early postnatal adaptation was observed in all newborns, in whose feces RV AG was defined, without clinical manifestations of RVI. Newborns had a higher weight loss, hyperbilirubinemia was recorded more often and for a longer period, the first breastfeeding took place after an average of 28.8 ± 5.9 hours.
RVI clinical manifestation was observed in newborns with hypoxic-ischemic CNS disorders, respiratory distress, conjugation hyperbilirubinemia, intrauterine hypotrophy, grade I-III, and anemia.
3. Frequency of RVI in newborns with perinatal pathology was 62.8% in full-term newborns, 67% in preterm children. Diagnostic RVI criteria in infants include: clinical (watery diarrhea, vomiting, bloating, enteral indigestion, dehydration class I-III., intoxication, respiratory manifestations); laboratory (presence of RV AG in feces in diagnostic titers 1: 16-1: 32, presence of antirotavirus serum antibodies in the titer 1:16, with the increase in the dynamics by 2-4 times).
4. RVI in newborns with perinatal pathology is characterized by considerable severity - 60.7% of severe and 35.7% of moderate forms in full-term infants, 62.3% and 37.7% in premature babies, respectively. Leading clinical symptoms include: intoxication (96.2%, 98.4% - in full-term and preterm babies, respectively) with hemodynamic disorders, diarrhea (81.5% vs 74%), vomiting, abdominal distension (59.3% vs 67, 5%), enteral indigestion (37% vs 20.8%), respiratory manifestations (51.9% vs 55.8%), and dehydration class I-III. (37% vs 42.9%).
5. In newborns with perinatal pathology in the conditions of neonatology departments, mixed RVI with more severe clinical forms prevails. The clinical course of mixed RVI in association with RV UPB and respiratory viruses is probably more severe compared to mono-RVI course due to the greater duration of diarrhea, vomiting, enteral indigestion, catarrhal symptoms and more severe temperature reaction.
6. RVI in newborns with perinatal pathology should be considered as a risk factor for the development of septic diseases. Nosocomial viral and bacterial complications are diagnosed in 51.9% of term and 46.8% in premature: sepsis (22.2% and 20.8%, respectively), UNE (29.6%, 31.2%), acute hematogenous osteomyelitis (18.5%, 9.1%), meningoencephalitis (3.7%, 5.2%), pneumonia (11.1%, 18.2%).
7. Widespread RVI risk factors in newborns have been established: chronic and acute urogenital infections, other infectious and extragenital pathology of the mother, chronic intrauterine fetal hypoxia, abnormal births, birth asphyxia, invasive measures of intensive care, late first breastfeeding, absence of colostrum period in physiological nursing and breastfeeding, artificial nutrition and tube feeding, antibiotic therapy, prolonged hospital stay are risk factors of microecological violations.
8. Improving adjuvant therapy, including administration of Laferon, Enterosgel, Simbiter, can increase clinical efficacy of treatment and promotes a more rapid normalization of clinical condition, namely reducing the duration of intoxication, gastrointestinal disorders, diarrhea, respiratory disorders and hyperbilirubinemia. The use of such a complex treatment reduces the accidence of septicopyemic foci in infants with mixed RVI, the incidence of UNE, pneumonia, sepsis, reduces secretion of RV with feces, as well as length of inpatient stay.

PRACTICAL RECOMMENDATIONS

Health Care Practice has proposed effective preventive measures based on the results of clinical and virological studies and determining RVI leading risk factors in infants.
In the practice of maternity and neonatology departments, specialized clinical virological and microbiological monitoring of RVI in newborns has been offered for early diagnosis and prevention of nosocomial RVI.
In complex care unit optimum schemes and methods of administration of recombinant interferon - Laferon in the dose of 50-100,000 IU / kg 2 times a day, in enemas, within 3-5 days has been offered; Enterosgel in the dose of 5 g / kg 3 times a day orally for 5 days. To correct microflora, multyprobiotic Symbiter was applied in RVI treatment in 0.5 dose twice a day, orally, for 10 days.

WORKS PUBLISHED ON DISSERTATION THEME

1. Shunko E.E., Dziublik I.V., Tunda I.P. Perinatal risk in the clinical course of rotavirus infection in newborns // Pediatrics, obstetrics and gynecology. – 1999. – No. 5. – p. 12-15.

2. Girin V.M., Dziublik I.V., Tunda I.P. Viruses causing gastroenteritis // Medical Journ. – 1999. – No. 5. – p. 3-7.

3. Shunko E.E., Dziublik I.V., Tunda I.P., Barbova G.I., Kovaliuk O.V. Rotavirus infection in the hospital according to epidemiology data // Ukr. Med. Journ. – 2000. – No. 5 (19). – p. 72-75.

4. Shunko E.E., Dziublik I.V., Tunda I.P., Starenka S.Ya. Modern therapies of rotavirus infection in newborns // Perinatology and pediatrics. – 2001. – No. 1. – p. 55-59.

5. Lab diagnostics of rotavirus infection. Girin V.M., Dziublik I.V., Shunko E.E., Voronenko S.G., Kiovalishin G.G., Blagodatny V.M., Werner O.M., Tunda I.P. // Methodical guidelines: – Kyiv, 2002. – 34 p.

6. Rotavirus infection: clinical performance, diagnostics and therapy. Shunko E.E., Dziublik I.V., Katoninas S.P., Kramarev O.S., Palatna L.O., Trohimenko O.P., Voronenko S.G., Tunda I.P. // Methodical guidelines: – Kyiv, 2003. – 25 p.

7. Tunda I.P. Various aspects of clinical rotavirus infection in newborns// Collection of works, Kyiv Postgraduate Academy named after P.L. Shupik in 1990-1996. – Kyiv. - 1990-1996. Kyiv, 1997 - p. 645-646.

8. Tunda I.P. Rotavirus infection in newborns (Review). // Collection of works for XX Anniversary Conference of young scientists, Kyiv Postgraduate Academy named after P.L. Shupik. – Kyiv – 1997. – p. 394-405.

9. Shunko E.E., Dziublik I.V., Tunda I.P. Risk factors of rotavirus infection in newborns. // Collection of works, Kyiv Postgraduate Academy named after P.L. Shupik. – Kyiv. – 1998. – p. 603-611.

10. Blagodatny V.N., Dziublik I.V. Shunko E.E., Kovaliuk E.V., Tunda I.P. DIC syndrome in rotavirus infection // Collection of works, Kyiv Postgraduate Academy named after P.L. Shupik. – Kyiv – 2000. – p. 1096-1104.

SUMMARY

Tunda I.P. Rotavirus infection in neonates: clinical course, treatment and prophylaxis. – Manuscript.

The dissertation for obtaining a scientific degree of the candidate of medical sciences in specialty 14.01.10.- "Pediatrics". National medical university named after O.O. Bogomolets, Kyiv, 2003.

The thesis is devoted to the issue of rotavirus infection in neonates and solves the problems of improving effectiveness of clinical diagnosis, treatment, prophylaxis of rotavirus infection.

The frequency and dynamics of detecting rotaviruses in neonates has been established, rotavirus infection clinical course particularities in neonates with perinatal pathology and in premature infants have been studied. The features of monorotaviral and associated infection forms have been investigated in comparative aspect. Major risk factors of infecting neonates by rotaviruses have been identified. A complex approach to treating neonates with rotavirus infection by using recombination interferon (laferon), enterosgel, correcting microecological disorders by using a multiprobiotic Symbiter has been improved. Effective prophylactic measures for rotavirus infection in neonates have been proposed.

Key words: neonates, rotavirus infection, clinical course, diagnostics, perinatal risk factors, prophylaxis.