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ETIOLOGICAL STRUCTURE, ANTIBACTERIAL RESISTANCE OF PATHOGENS AND CLINICAL COURSE OF HOSPITAL PNEUMONIA IN PREMATURE INFANTS

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ABSTRACT

We conducted a study of the etiological structure of nosocomial "ventilator-associated" pneumonia (VAP) and the clinical course of the disease in 100 premature newborns. There were revealed violations of the respiratory and cardiovascular systems, kidneys, the development of infectious toxicosis, changes in peripheral blood and urine. Possible complications are identified. VAP pathogens were represented by gram-positive and gram-negative bacteria, as well as Candida spp. The cause of nosocomial pneumonia were associations of 2 and less often 3 types of bacteria in 35% of premature infants. 39.4% of newborns developed a secondary infection with a change in pathogen. At the same time, *Pseudomonas aerugimosa*, *Stenotrophomonas maltophilia*, coagulase-negative *Staphylococcus*, *Klebsiella pneumoniae* were most often isolated. More than half of the bacteria were resistant to many antibiotics and retained sensitivity only to individual drugs.

KEYWORDS: Nosocomial pneumonia, etiology, antibiotics, premature newborns, clinical course.

INTRODUCTION

Among infectious and inflammatory diseases in newborns, a special place is occupied by "ventilator-associated" pneumonia, which develops against the background of the use of mechanical artificial lung ventilation (ALV). By analogy with the same pneumonia in adults, they were called "Ventilator-associated pneumonia" ("VENT-associated pneumonia" or "VAP").[1,2,3]

VAP develops in a patient 48-72 hours or more after endotracheal intubation and the start of mechanical ventilation due to respiratory failure not associated with pneumonia. Neonatal pneumonia often has serious consequences and a fatal outcome. This disease can be complicated by the development of sepsis, meningitis, bronchopulmonary dysplasia, and also contribute to the formation of chronic lung diseases in infants, leading to disability.[4,5,6,7] VAP significantly lengthens the period of stay of infants in the hospital, i.e. cause great economic damage, which determines not only the medical but also the social significance of the problem. The frequency of such pneumonia is according to different authors from 10 to 48%.[6,8,9]

Studies conducted in our clinic have shown that the incidence of VAP in preterm infants is on average 37.5%. Moreover, it was the highest (85%) in infants with severe respiratory distress syndrome (RDS) and weighing less than 1500 g. At the same time, it was 48.5% in similar infants weighing more than 1500 g. The development of pneumonia was observed in 25% of cases in infants on mechanical ventilation due to neurological disorders, and in the syndrome of amniotic fluid aspiration, mainly in full-term infants - 13%.[3,6,7]

The role of ALV in the development of complications is determined by the fact that in this case there is a wider access to the surrounding microorganisms for penetration into the lower respiratory tract, since the standing of the endotracheal tube turns off a significant area of local anti-infective protection. In addition, it is known that inhaled oxygen can have a detrimental effect on respiratory epithelial cells, making them more vulnerable to infection.[1,2,9,10]

Thus, despite the great attention given to prevention and treatment of infectious and inflammatory diseases in infants, the problem of VAP in neonatology remains relevant.

The outcome of the disease depends on a timely diagnosis and the right treatment. The basis of the treatment of nosocomial pneumonia is antibiotic therapy, the success of which is largely determined by the correctly chosen starting empirical therapy (based on the analysis of microbiological monitoring in a particular hospital and in the region).

Considering all of the above, the purpose of this study was to determine the etiological structure and features of the clinical course of VAP in preterm infants.

MATERIAL AND METHODS

Under observation were 100 premature infants with VAP, whose birth weight ranged from 680 to 2660 g, and gestational age from 24 to 37 weeks. All infants were on ALV from birth for respiratory failure. All infants, along with an analysis of the clinical condition, underwent special microbiological studies of tracheobronchial aspirate by standard culture to identify aerobic and facultative microflora. The number of microorganisms isolated from the tracheobronchial aspirate was expressed as a decimal logarithm (lg|ml) in 1 ml of aspirate. The number of microbial cells equal to lg4/ml and above was considered etiologically significant.[11] Determination of the sensitivity of microorganisms to antibiotics was carried out by the method of diffusion in agar using standard sets of discs (Research Center for Pharmacotherapy, St. Petersburg).[12]

Statistical processing of the obtained data was carried out using the Microsoft Office application packages for statistical processing of Microsoft Excel (version 9.0) and the Statistica 6.0 program. From the data set, we calculated the frequency of occurrence of the trait in %, the mean of the variational series (M), the standard deviation, the error of the mean (m), Student's t test.

RESULTS AND DISCUSSION

All babies were born prematurely in women with burdened somatic and obstetric-gynecological anamnesis. Chronic somatic pathology (bronchial asthma, bronchitis, pyelonephritis, gastritis, etc.) was observed in 65% of mothers, and chronic gynecological diseases (infertility, adnexitis, cervical erosion, colpitis, endometritis, etc.) occurred in 50%. Complicated course of pregnancy in the form of toxicosis in the I and II halves was observed in 39% and 34%, respectively. Complication of childbirth in the form of prenatal rupture of amniotic fluid was observed in 23% of mothers, placental abruption and bleeding during childbirth - in 10%, chorioamnionitis - in 3%.

All infants were born in a serious condition, which in 65 infants was due to respiratory distress syndrome, in 20 newborns - amniotic fluid aspiration syndrome and in 15 - hypoxic lesions of the central nervous system (CNS). 56 newborns were born in asphyxia with an Apgar score of less than 6 points. Most infants developed severe pneumonia on the 5-7th day of life, the diagnosis of which was confirmed on the basis of anamnesis data, clinical, radiological and laboratory examination methods.

Common to all infants was that, firstly, the onset of pneumonia in them was preceded by syndromes of impaired early postnatal adaptation of respiration, the cardiovascular system and the central nervous system, and, secondly, that pneumonia developed in ALV conditions with elevated oxygen concentrations and inspiratory pressure. Characteristics of the clinical course of VAP are presented in tables 1-3.

In most infants, the onset of pneumonia is in the first week of life (72). In the clinical picture, this was manifested by the appearance of symptoms of infectious toxicosis, increased respiratory failure, an increase and a change in the nature of physical changes in the lungs. The ventilation parameters became insufficient for adequate ventilation. Often, especially in infants weighing ≤1500 g, a systolic heart murmur was heard during this period, arterial pulsation, tendency to tachycardia, which indicated blood shunting through the open ductus arteriosus. A severe form of the disease was observed in most infants (64), moderate - in 36. Acute course was in 78 infants, protracted - in 22.

Attention was drawn to the clinical signs of infectious toxicosis (table 1), namely, the appearance of gray color and "marble" skin pattern, changes in the CNS in the form of a significant inhibition of physiological reflexes, including such persistent ones as sucking and nasopalpebral, motor activity and muscle tone. The CNS stimulation was also noted. There was a tendency to hypothermia (in 15), a short-term increase in body temperature in the range of 37.5 - 38.2^0 C (in 40), hepatomegaly, splenomegaly, leukocytosis (mean leukocyte count 26.86±3.0 x 10^9/l), increase in the content of ALT and AST transaminases in the blood. 6 infants had convulsive readiness and convulsions.

Changes in the respiratory and cardiovascular systems are presented in Table 2. Respiratory failure was manifested by an increase in pCO_2 (average 59 ± 4.5 mm Hg), a decrease in pO_2 (46.5 ± 3.3 mm Hg), a decrease in the level of Hb to an average of 96±1.19 g/l and SaO_2 - 85±2.2%. The duration of respiratory failure in infants usually ranged from 25 to 40 days. There were changes in the cardiovascular system in the form of a weakening of the heart sounds in 60 infants, an increase in its boundaries, the development of edema, tachycardia in 30 infants and bradycardia in 7. Changes in the lungs were always bilateral and were characterized by the presence of a shortened percussion sound, abundant widespread wet and crepitant rales in the lungs. Most infants had manifestations of tracheobronchitis lasting from 16 to 36 days.

On radiographs, bilateral lung damage was determined in most cases (in 47 infants) in the form of large-focal areas of decreased pneumatization, increased bronchovascular pattern. Drain pneumonia occurred in 8 infants. In 20 infants, along with focal shadows, edematous changes, segmental or widespread, were determined. 25 infants had lobar atelectasis, 9 had pneumothorax, and 2 had interstitial air.

Changes in the lungs were combined with pathological symptoms from other organs and changes in laboratory parameters. High leukocytosis, including neutrophilia (in 61), thrombocytopenia (in 19), anemia (in 64) were noted in the peripheral blood of 70 infants. Toxic granularity of neutrophils was detected in 11 infants. The level of C-reactive protein was elevated in 16 infants and averaged 21.2±3.8 mg/l at a rate of up to 6 mg/l. There was a decrease in serum potassium concentration in 4 infants, calcium also in 4 infants, and sodium was reduced in 14 newborns. The content of direct bilirubin in the amount of more than 10-15% of the total was noted in 11 infants.

Kidney dysfunction was detected in the form of a decrease in diuresis in the first days of illness (<1-2 ml/kg/h) in 15 infants, an increase in the level of urea (in 23), and creatinine (in 8) in the blood serum. Edema syndrome was observed in 20 newborns. Pathological changes were observed in the analysis of urine, in the form of proteinuria - in 43 infants, leukocyturia - in 41, microhematuria - in 28 and bacteriuria - in 13. Candida spp. was found in 7 infants. A large initial loss of body weight (more than 15% in 27 newborns) also indicated the severity of the condition and the unfavorable course of adaptation processes.

Table 1: Clinical manifestations of infectious toxicosis in the acute period of nosocomial pneumonia in 100 premature newborns.

N	Clinical symptoms	Total number of infant (n=100)	
		Number of symptomatic infants (n)	%
1	Depression of the central nervous system	20	20
2	Excitation of the central nervous system	18	18
3	Hypothermia	15	15
4	Single or short-term increase in body temperature	40	40
5	Gray skin tone	58	58
6	“Marbling” of the skin	54	54
7	Hepatomegaly	39	39
8	Splenomegaly	23	23

Table 2: Changes in the respiratory and cardiovascular systems in 100 premature newborns in the acute period of nosocomial pneumonia.

№	Clinical symptoms	Number of symptomatic infants (n)	%
1	Diffuse cyanosis	3	3
2	Cyanosis localized	97	97
3	Attacks of asphyxia and cyanosis	20	20
4	Increased respiration 51-100 per minute	95	95
5	Increased chest rigidity	40	40
6	Shortening of percussion sound	90	90
7	Persistent profuse moist rales in the lungs	85	85
8	Dry wheezing	10	10
9	Tracheobronchitis	78	78
10	Acid-base status (ABS) data: metabolic acidosis	30	30
11	ABS data: respiratory acidosis	49	49
12	ABS data: mixed acidosis	18	18
13	pCO_2 in the blood (mm Hg) (M ± m)	59,0±4,5	-
14	pO_2 in the blood (mm Hg) (M ± m)	46,5±3,3	-
15	Pulmonary bleeding	15	15
16	Tachycardia	30	30
17	Bradycardia	7	7
18	Decreased heart sounds	60	60
19	Systolic murmur	25	25

Table 3: Characteristics of the clinical course of nosocomial pneumonia in premature newborns.

N	Clinical indicators	Total number of infant (n=100)
1	Duration of pneumonia, days (M±m)	33,6±4,1
2	Duration of severe condition, days (M±m)	30,96±2,47
3	Duration of infectious toxicosis, days (M±m)	23,55±3,04
4	Duration of wheezing in the lungs, days (M±m)	33,6±2,34
5	Duration of respiratory failure, days (M±m)	32,53±2,51
6	Length of stay in the oxygen tent, days (M±m)	22,12±1,8
7	The duration of the infant's stay in the incubator, days (M±m)	33,12±1,99
8	Tube feeding duration, days (M±m)	30,18±2,32
9	Positive dynamics of body weight (since what day of life) (M±m)	24,29±2,68
10	Length of stay of the infant in the hospital (bed-day) (M±m)	42,15±1,35

The acute course of pneumonia (1–1.5 months) was in the majority of newborns (78), protracted - in 22 infants, in whom the duration of the disease was more than 50 days (33.6±4.1 days). Complications in the form of atelectasis were observed in 25 infants, pneumothorax in 9 infants, bronchopulmonary dysplasia in 8 infants, pleurisy in 1 infant, and sepsis in 5 infants.

The main parameters characterizing the course of VAP are presented in the table 3. Duration of pneumonia, on average, was more than a month. It was characterized by a long course of infectious toxicosis, respiratory failure. The need for oxygen supplementation, tube feeding and stay in the incubator were also prolonged. Auscultatory changes in the lungs, as well as a serious condition, persisted on average for more than a month.

The overall mortality was 17%. The length of stay in the hospital for surviving infant ranged from 30 to 65 days.

Studies have shown that the etiological structure of nosocomial pneumonia in premature infants is represented by a wide range of microorganisms. *E.coli* was found in 26% of patients, *Klebsiella pneumoniae* - in 21%, *Ervinia amilovora* - in 5%, *Enterobacter cloacae* - in 5%, *Plesiomonas shigeloide*s - in 2%, *Serracia marcescens* - in 2%, *Pseudomonas aeruginosa* (*Ps. aeruginosa)* - in 35%, *Stenotrophomonas maltophilia* - 14%, *Acinetobacter baumannii* - 6%, *S. epidermidis* (coagulase-negative *Staphylococcus*) - 30%, methicillin-resistant *S. aureus* (MRSA) - 4%, *Enterococcus faecalis* - 17%, *Streptococcus spp.* - in 4%, *Candida albicans* - in 4%.

Quite often, associations of 2 and less often 3 pathogens were the cause of nosocomial pneumonia in premature newborns. These were combinations of *Enterobacteriaceae* bacteria with Gram-positive cocci (in 14%) and/or *Pseudomonas spp*. (in 8%), as well as Gram-positive cocci with *Pseudomonas* spp. (in 7%). Associations of gram-positive cocci with other gram-negative microorganisms occurred in 2% of newborns, and the combination of two species of *Enterobacteriaceae spp*. - 1%. The combination of bacteria and fungi was observed in 4% of newborns. Quite often, associations of 2 and less often 3 pathogens were the cause of nosocomial pneumonia in premature newborns.

A feature of the etiological characteristics of nosocomial pneumonia in premature newborns was a high frequency of pathogen change in the dynamics of observation after an average of 10.0 ± 0.81 days, with fluctuations from 5 to 14 days (in 39.4% of infant). This is accompanied by a worsening of the clinical course of the disease. At the same time, *Ps. aerugimosa*, *Stenotrophomonas maltophilia*, coagulase-negative *Staphylococcus*, *Klebsiella pneumoniae* were the most frequently isolated.

Conducting a study of the sensitivity of microorganisms to antibiotics, as well as biochemical and serological properties, showed that they belong to hospital strains. These strains were characterized by the presence of pathogenicity factors (hemolytic activity, elastase, phospholipase, gelatinase activity, the ability to produce DNAse, plasmacoagulase, and various toxins). These enzymes had a damaging effect on the tissues of the infant's body, causing damage and cell death, and contributed to the development of inflammation and intoxication. Powerful production of pro-inflammatory cytokines in response to pathogen invasion and endogenous intoxication associated with hypoxia exacerbated the situation.[13-16]

Most of the isolated microorganisms were resistant to many antibiotics and retained sensitivity to some drugs. In particular, *Ps. aerugimosa* was sensitive to aminoglycosides (amikacin, gentamicin), fluoroquinolones (ciprofloxacin, ofloxacin), colistin; *Stenotrophomonas maltophilia* - to ceftazidime, ciprofloxacin, chloramphenicol; *Klebsiella pneumoniae* - to aminoglycosides (amikacin, netilmicin), cefotaxime, imipenem; *Enterobacter cloacae* and *Ervinia amilovora* were sensitive to amikacin, ciprofloxacin and imipenem.

All isolated strains of gram-positive cocci were sensitive to vancomycin, and from 28 to 50% of the strains were sensitive to other antibiotics: *S. epidermidis* - to vancomycin, linezolid, rifampicin, *S. aureus* - to vancomycin, linezolid, macrolides (erythromycin, macropenes), fusidin-natrium, cefotaxime, *Enterococcus spp*. - to vancomycin, linezolid, imipenem and

rifampicin. Only *E. coli* strains remained sensitive to most of the antibiotics used (III-IV generation cephalosporins, aminoglycosides, as well as carbapenems, fluoroquinolones).

Initial therapy was represented by various treatment regimens that covered the spectrum of possible bacterial pathogens of nosocomial pneumonia. These were combinations of III generation cephalosporins with aminoglycosides or glycopeptides, aminoglycosides with glycopeptides, semisynthetic penicillins with aminoglycosides or glycopeptides, as well as monotherapy with II-III generation cephalosporins. Antibiotic treatment continued in the future, taking into account the microbiological examination.[1,3,9,10] All patients, along with antibiotics, received immunoreplacement therapy with intravenous immunoglobulins, oxygen therapy, parenteral nutrition, and correction of homeostasis disorders. The obtained results of the sensitivity of strains to antibiotics are consistent with the results of many researchers who pay attention to the wide prevalence of multidrug-resistant pathogens in hospitals and the need to take into account the antibacterial spectrum in a particular hospital and department when choosing initial therapy.[8-10] The use of III generation cephalosporins + amikacin, carbapenems + amikacin in our clinic showed a good clinical effect in VAP caused by gram-negative bacteria. Vancomycin and linezolid were effective in VAP caused by gram-positive pathogens, including *Enterococcus spp*., *S. aureus* and coagulase-negative *Staphylococcus*, which is consistent with the data of other.[17-19]

CONCLUSION

VAP in premature infants on mechanical ventilation in most cases develops on the 1st week of life against the background of already existing morphological and functional changes in the lungs.

The development of VAP is closely related to unfavorable conditions of intrauterine development, burdened anamnesis in mothers, complications during pregnancy and childbirth, as well as disorders of postnatal adaptation of respiration, cardiovascular and central nervous systems.

The combination of previous pneumonia clinical manifestations of early adaptation disorders with the development of an infectious process causes the formation of severe forms of the disease in most premature infants, which occur with severe toxicosis, trophic disorders, severe respiratory failure, bilateral, more common damage to the lungs and respiratory tract (tracheobronchitis), frequent occurrence atelectasis, pneumothorax, bronchopulmonary dysplasia and high mortality.

The noted clinical features of nosocomial pneumonia developing on the background of mechanical ventilation in newborns can be used to diagnose this disease and determine the type of therapy.

The etiological structure of VAP is represented by a wide range of gram-positive and gram-negative aerobic and facultative bacteria. Often there are associations of pathogens, as well as secondary infection with hospital strains of microorganisms. Antibiotics for treatment should cover the susceptibility spectrum of possible VAP pathogens.

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