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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

ALT SOLUNUM YOLU ENFEKSİYONU TANISI İLE YENİDOĞAN YOĞUN BAKIM ÜNİTESİNE YATIRILAN OLGULARIN DEĞERLENDİRİLMESİ

ASSESSMENT OF CASES ADMITTED TO THE NEONATAL INTENSIVE CARE UNIT WITH LOWER RESPIRATORY TRACT INFECTION

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ÖZET

AMAÇ: Bu çalışmanın amacı, alt solunum yolu enfeksiyonu (ASYE) tanısıyla yenidoğan yoğun bakım ünitesine yatırılan bebeklerin klinik özelliklerinin ve laboratuvar bulgularının, tanı ve tedavilerinin değerlendirilmesidir.

GEREÇ VE YÖNTEM: Hastanemizde 2017 - 2019 tarihleri arasında yenidoğan yoğun bakım ünitesine ASYE tanısı konularak yatırılan bebeklerin verileri retrospektif olarak dosya kayıtlarından elde edildi. Demografik özellikleri, tanı ve tedavileri analiz edildi.

BULGULAR: Çalışmaya ASYE tanısı alan toplam 57 hasta dahil edildi. Hastaların ortalama gestasyon yaşı 36.8±3 hafta, ortalama doğum ağırlığı 2864±787 g idi. % 67 (n=38)'si term, % 33 (n=19)'ü preterm bebekti. Olguların başvuru anındaki semptom, muayene bulguları ve akciğer grafileri incelendiğinde; %67 (n=38)'inde takipne, ekspiryumda uzama ve beslenme güçlüğü, %26 (n=15)'sında öksürük, %20 (n=12)'sinde ateş, %12 (n=7)'sinde kusma, %7 (n=4)'sinde apne, %21 (n=12)'inde akciğer grafisinde havalanma artışı saptandı. Hastaların %61 (n=35)'inde nazofarengeal sürüntü örneklerinde PCR yöntemi ile solunum paneli bakıldı, bunlarında %57 (n=20)'sinde Respiratuvar sinsityal virüs (RSV) enfeksiyonu, %14 (n=5)'ünde Rhinovirüs, %3 (1)'ünde Metapnömovirüs pozitif saptandı. Hastaların %47 (n=27)'si yüksek akımlı oksijen, %26 (n= 15)'sı nazal CPAP, %58 (n=33)'i antibiyotik, % 63 (n= 36)'ü inhaler bronkodilatör ve hipertonik salin tedavisi aldı.

SONUÇ: Hastanemizde ASYE tanısı ile yatırılan olgularda literatürle uyumlu olarak yüksek oranda RSV enfeksiyonu saptandı. Tanının erken konulması, gereksiz antibiyotik kullanımı ve nozokomiyal enfeksiyonları önlemek açısından önem taşımaktadır.

ANAHTAR KELİMELER: Yenidoğan, Polimeraz zincir reaksiyonu, Respiratuvar sinsityal virüs, Solunum yolu enfeksiyonları

ABSTRACT

OBJECTIVE: The purpose of this study is to assess the clinical features, laboratory findings, diagnosis and treatments of neonates in the neonatal intensive care unit with a diagnosis of lower respiratory tract infection (LRTI).

MATERIAL AND METHODS: The data of neonates hospitalized in the neonatal intensive care unit of our hospital between 2017 and 2019 with a diagnosis of LRTI was retrospectively obtained from the file records. Demographical features, diagnosis and treatments were analyzed.

RESULTS: A total of 57 patients diagnosed with LRTI were included in the study. The mean gestational age of the patients was 36.8 ± 3 weeks and their mean birth weight was 2864 ± 787 g. The 67% (n = 38) of them were term infants and the 33% (n = 19) of them were preterm infants. When the symptoms, examination findings and chest radiographs of the cases were examined at the time of admission, tachypnea, prolonged expiration, and nutritional difficulty in 67% of cases (n = 38), cough in 26% (n = 15) of the cases, fever in 20% (n = 12) of the cases, vomiting in 12% (n = 7) of the cases, apnea in 7% (n = 4)of the cases, and increased aeration in lung imaging in 21% (n = 12) of the cases were detected. Respiratory panel using Polymenase Chain Reaction (PCR) method was investigated in nasopharyngeal swab samples of 61% (n = 35) of the patients, respiratory syncytial virus (RSV) in 57% (n = 20), rhinovirus in 14% (n = 5), and metapneumovirus in 3% (n = 1) of the cases were observed. The 47% of the patients (n = 27) received high-flow oxygen, 26% (n= 15) nasal CPAP, 58% (n=33) antibiotics, 63% (n= 36) inhaler bronchodilator and hypertonic saline treatment.

CONCLUSIONS: In accordance with the literature, a high rate of RSV infection was detected in neonates with LRTI in the neonatal intensive care unit of our hospital. Early diagnosis is important to prevent unnecessary use of antibiotics and to prevent nosocomial infections.

KEYWORDS: Newborn, Polymerase chain reaction, Respiratory syncytial virus, Respiratory tract infections

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INTRODUCTION

Lower respiratory tract infection (LRTI) is one of the main causes of mortality and morbidity of neonates and breastfed infants all over the world. According to the report published by the World Health Organization in 2015, LRTI is responsible for the death of 15% of children under five years old in our country and the death of 9% of the children under five years old in the world (1). The most common causes of LRTI are viruses. Respiratory syncytial virus (RSV), parainfluenza virus (PIV) type 1, 2, 3, influenza A, influenza B, rhinovirus, and adenoviruses are the most common viruses causing LRTI during infancy (2). These infections incur a heavy burden to the national health budget due to the mortality and morbidity they cause. Since viral and bacterial pneumonia cannot be always distinguished both clinically and radiologically, the investigation of viral etiology is important to avoid unnecessary use of antibiotics and to implement antiviral treatment and vaccination against some viruses and on some selected patients (3).

In this study, assessment of clinical features, diagnosis, and treatments of neonates with LRTI and hospitalized in neonatal intensive care unit were studied.

MATERIAL AND METHOD

LRTI diagnosed neonates hospitalized in the neonatal intensive care unit (NICU) of our hospital between January 2017 - December 2019 were included in this study. Patient data were obtained retrospectively from the NICU patient files.

The demographical features, clinical findings and laboratory data of the neonates, and demographical features of maternal, pregnancy and labor complications were investigated.

The gestational ages, birth weights, 1st and 5th minute scores, sex, Apgar scores, mode of delivery, the need of hospitalization after birth, physical examination findings; tachypnea cough, wheezing and prolonged expiration, cough, fever (>37.8C°), feeding difficulties, vomiting, apnea were assessed from the files. In the laboratory data, leucocyte, platelet, hemoglobin, hematocrit, C-reactive protein values and respiratory panel using PCR method in nasopharyn geal swab (multiplex real-time PCR scanning kit) results were analyzed. Influenza A, Influenza B, Bocavirus, Enterovirus, Human Parechovirus, Adenovirus, Coronavirus, Metapneumovirus, Respiratory Syncytial Virus A/B, Rhinovirus, Parainfluenza were investigated in the respiratory panel. Leucocytes >15000/mm^3 and C-reactive protein>0.5mg/dl were accepted as high. Chest x-rays were assessed in terms of infiltration and inflation increase in the lungs. The treatment given to patients were grouped as antibiotics, inhaled bronchodilators and hypertonic saline, oxygen, high flow oxygen, nasal continuous positive airway pressure (CPAP), and mechanical ventilation. Hospitalization periods were recorded. In addition, the cases that had >7 days of hospital stay were accepted as lengthy-hospital-stay patients. In order to find out the reasons for a lengthy hospital stay, the cases whose hospital stay days are >7 days were compared with those who had ≤7 days of hospital stay in terms of the demographic features of mothers and neonates. Patients with missing data were not included in the study. Since the study is retrospective and the data was scanned out of the files, informed consent forms were not taken.

Ethical Committee

This study was approved by the Istanbul Medeniyet University, Goztepe Training and Research Hospital Ethics Committee for Clinical Studies, 2020/0090.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) version 20 (SPSS Inc.; Chicago, Il, USA) software was used for statistical analysis. Descriptive statistics and frequency distributions of the variables were calculated. Continuous variables were presented as mean±standard deviation whereas categorical variables were presented as percentages. Categorical variables were compared using the Chi-square test, or where appropriate, Fisher's exact test. Student T-test or Mann-Whitney U test was used to compare the continuous variables after testing for normal distribution. A double-sided p-value <0.05 was accepted as significant.

RESULTS

There were 1548 neonatal admissions to our neonatal intensive care unit during the years 2017-2019. 3.9% (n=61) of these were hospitalized with the diagnosis of lower respiratory tract infection (LRTI). Four of these neonates were excluded from this study due to their missing data. The study population consisted of 57 neonates aged 7 – 94 days diagnosed with LRTI. The demographic features of neonates hospitalized with LRTI are shown in **Table 1**.

Table 1: Demographic characteristics of the neonates

Variables	n= 57
Gestational age (weeks)	36.8±3
Birth weight (gram)	2864 ± 787
Cesarean delivery	38 (67)
Preterm	19 (33)
Term	38 (67)
Gender (male)	31 (54)
Small for gestational age	4 (7)
Respiratory distress syndrome	4 (7)
Transient tachypenea of newborn	3 (5)
Hyperbilirubinemia	3 (5)
Esophageal atresia	3 (5)
Postnatal age at admission (day)	29 ± 19
Duration of hospitalization (day)	7 ± 2.7

Data are presented as mean±SD and n (%) values

The mean gestational age was 36.8 ±3 weeks (range, 29 – 41 weeks) and the mean birth weight was 2864 ± 787 g (range, 1230 – 4210 g). The study population consisted of 67% (n = 38) term infants and 33% (n = 19) preterm infants, 67% (n=38) were born by cesarean delivery, and 54% (n = 31) were male. There was respiratory distress syndrome in four cases, transient tachypnea of newborn in three cases, hyperbilirubinemia in three cases, and esophageal atresia in three cases. The mean maternal age was 28.9±6.1 years.

Three mothers had Preeclampsia, two had placenta previa, one had placenta decolman, three had gestational diabetes, two had hyperthyroid, and five had smoked in their history. Diagnostic findings and chest x-ray findings at the time of presentation indicated tachypnea, prolonged expiration, and feeding difficulty in 67% of cases (n = 38), cough in 26% (n = 15), fever in 20% (n = 12), vomiting in 12% (n = 7), apnea in 7% (n = 4), increased aeration in chest x-ray in 21% (n = 12) and, infiltration in 11% (n=6). CRP positivity in 25% and leukocytosis in 26% of the neonates were identified. Respiratory PCR panel examination was performed using nasopharyngeal swab samples in 61% (n = 35) of the patients and revealed respiratory syncytial virus (RSV) infection in 57% of cases (n = 20), rhinovirus infection in 14% (n = 5), and metapneumovirus infection in 3% (n = 1). Among the RSV-positive patients, 65% (n = 13) were preterm neonates **(Table 2)**.

Table 2: Physical examination, lung imaging and laboratory findings of the neonates

Physical examination	n (%)
Tachypnea	38 (67)
Prolonged expiration	38 (67)
Feeding difficulty	38 (67)
Cough	15 (26)
Fever	12 (20)
Vomiting	7 (12)
Apnea	4 (7)
Chest X-ray	
Increased aeration	12 (21)
Infiltrations	6 (11)
Laboratory findings	
High leukocytosis (>15000/mm^3)	15 (26)
C-reactive protein positive (>0.5)	14 (25)
Virus scan by the PCR method	35 (61)
RSV positive	20 (57)
Rhinovirus positive	5 (14)
Metapneumovirus positive	1 (3)

Data are presented as n (%) values

High-flow oxygen was applied in 47% of the patients (n = 27), 26% (n = 15) received CPAP, 58% (n = 33) received antibiotics, and 63% (n = 36) received inhaler bronchodilator and hypertonic saline treatment **(Table 3)**.

Table 3: Treatment type of the neonates

Treatment type	n (%)
Inhaled bronchodilators and nebulized hypertonic saline solution	36 (63)
Antibiotics	33 (58)
High-flow oxygen	27 (47)
Nasal continuous positive airway pressure	15 (26)
Ventilation support	2 (3.5)

Data are presented as n (%) values

The mean period of hospitalization in the NICU was 7± 2.7 days. In addition, the cases whose hospital stay days are >7 days were compared with those who had ≤7 days of hospital stay.

No significant difference was identified between the two groups in terms of gestational age,

birth weight, low birth weight (<2500 grams), sex, way of birth, maternal age, smoking during pregnancy **(Table 4)**. All infants were discharged from the hospital in our study.

Table 4: Demographic characteristics of long-term hospitalized neonates and short–term hospitalized neonates

	Hospitalization		p
	≤7 days (n=35)	>7days (n=22)	
Gestational age (weeks)	37.1±3.3	36.4±2.42	0.12
Preterm	9 (47.4)	10 (52.6)	0.12
Gestational age (<32 weeks)	5 (71.4)	2 (28.6)	0.70
Birth weight (gram)	2903±817.3	2802.2±752.5	0.46
Low Birth weight (<2500 gram)	12 (60)	8 (40)	0.87
Gender (male)	23 (74.2)	8 (25.8)	0.03
Cesarean delivery	24 (63.2)	14 (36.8)	0.70
Need of hospitalization after birth	10 (47.6)	11 (52.4)	0.10
Maternal age, (years)	28.4±6.8	29.6±4.7	0.36
Smoking in Pregnancy	5 (100)	0 (0)	0.15

Data are presented as mean±SD and n (%) values

DISCUSSION

RSV is the most frequently observed respiratory tract infection agent in neonates and infants worldwide. Following the neonatal period, it is the second most common cause of infant deaths after malaria (4). Its prevalence is 5.2/1000, and 26/1000 in neonates younger than one-month-old (5). Hacimustafaoglu et al. (6) reported that in 671 LRTI inpatients under 24 months, RSV prevalence was identified as 37.9 % of whom 0-3 month infants constituted 38.3%. In the study of Turkish Neonatal Society (7) which included 3464 patients under 24 months and hospitalized with LRTI diagnosis and who did not receive RSV prophylaxis, RSV prevalence was found to be 16.9%, was seen that RSV infection peaked in 0-3 months and during January-March. In our study as well, a high rate of RSV positivity was detected in neonates who were hospitalized with LRTI diagnosis and who were monitored for the respiratory panel in their nasopharyngeal swab samples using the PCR method for etiology. Every year, RSV infection causes 48.000-74.500 deaths in < 5-year-old infants and 99% of RSV-related deaths occur in developing countries (8). The neonatal mortality rate is 2-3%, the mortality rate between one-month-olds and one-year-olds is 6-7% (9).

In the multi-center study of Alan et al. (10), the rate of RSV-related mortality is reported as 1.2% in our country. All infants were discharged from the hospital in our study. Clinical findings may range from mild upper respiratory tract infection or otitis media to life-threatening lower respiratory tract infections. RSV, especially in winter, causes serious LRTI in infants and young children and it is considered the most common reason for bronchiolitis and pneumonia during infancy (11). 87 % of all infants younger than 18 months and 100% of all infants younger than the age of 3 years are infected with RSV (12).

Although antibodies against RSV develop in the following years, reinfections with RSV may occur (13). The first six-month period is critical and the most severe disease is observed then (5).

Being under 2 years old, low birth weight, prematurity, the existence of an underlying chronic disease, lack of breastfeeding, malnutrition, hypovitaminosis D, low socioeconomic status, crowded areas, winter season, lack of health services, active and passive smoking, air pollution, and inadequate immunization are the risk factors for RSV infection (14, 15). Besides, boys are twice more sensitive to LRTI as compared to girls. This can be explained by the fact that boys have narrower airways during the first months of life (16). Similarly, in our study 54% of the hospitalized infants were boys.

Rhinovirus infection in 14% and metapneumovirus infection in 3% positivity were detected in neonates with LRTI diagnosis in our study. Okulu et al. (17), reported that in 81 neonates who were admitted to Neonatal Intensive Care Unit (NICU) with LRTI, rhinovirus prevalence was found as 6%. While RSV is the most common factor for bronchiolitis in young children, rhinovirus is a factor in the exacerbation of asthma in older children (18). In a study by Sancaklı et al. (19), human metapneumovirus was identified 6.9% in children with LRTI.

Just like RSV, metapneumovirus causes colds, bronchiolitis, and pneumonia in newborns, but less frequently. In patients with viral lower respiratory tract infection, a runny nose starts first followed by cough, mild fever, and wheezing. If progressive, cough and wheezing increase, air hunger and retractions start, frontal and rear diameter of the chest increases, tachypnea, cyanosis, and apnea attacks develop (20). In our study, the most common symptoms in LRTI patients were found to be tachypnea, prolonged

expiration, and feeding difficulty. RSV is generally self-remitting and rarely causes death in normal infants. However, disease and death rates increase severely in patients with congenital heart disease, chronic lung disease, inadequate immunization, hypoxia, and who are premature or less than 6 weeks old (21). 57% of the RSV-positive patients in our study were preterm babies and the gestation age of 88% of them was between 30-35 weeks. This result shows that immunoglobulin prophylaxis is important because the RSV positivity rate is high in those who have a history of premature birth and in those who did not receive immunoglobulin prophylaxis.

In the diagnosis of RSV infection, laboratory tests are non-specific. The complete blood count is not specific. There may be a mild increase in C-reactive protein (CRP). In chest x-ray, increased inflation, a flattened diaphragm, infiltrations, patchy atelectasis, and increased peribronchial shades may be observed. The National Institute for Health and Care Excellence (NICE) (22) recommends the RSV diagnosis to be made with detailed patient history and physical examination, laboratory and radiological tests for severe bronchiolitis cases which necessitates hospitalization in intensive care unit or for atypical bronchiolitis cases. The number of white blood cells may be normal or high in RSV-infected patients (2, 23). In our study, leukocytosis was observed in 26% and CRP positivity was observed in 25% of the LRTI patients, CRP positivity was in 40% and leukocytosis was in 13% of RSV positive patients. Our study supports that acute phase reactants increase viral infections. Although most chest x-rays were non-specific, hyperinflation was identified in 21% and infiltration was identified in 11% of our patients.

Viral bronchiolitis is a self-limiting disease in most infants and there is generally no need for a test of RSV or other pathogens. Rapid diagnosis of a virus, for definitive diagnosis, especially for inpatients, should be carried out to decrease empirical antibiotics and to prevent nosocomial contamination, isolation, and infection control (24). The gold standard for RSV diagnosis is viral culture but in nasal secretions, polymerase chain reaction (PCR) or RSV antigen with immunofluorescence method may also be used. The sensitivity of these methods with respect to culture is 50-96% (frequently 80-90%) (25, 26). Routine RSV culture is not carried out in our country. In our study, the nasal secretion aspiration samples were studied with the PCR method.

Viral LRTI treatment is supportive and includes regulating the oxygenation of the patient, providing nutrition and hydration, and close monitoring of the patient in terms of complications. Acting quickly in the treatment of symptoms may cause unnecessary use of antibiotics, steroids, or inhaled bronchodilators. According to the guide published by American Pediatrics Academy in 2014 (27) and the NICE guide (19), treatments other than nutrition and oxygen support are not effective. An inhaled bronchodilator is not routinely recommended for Viral LRTI patients. Bronchodilators can be tried if there is an individual or family atopy history or wheezing is the most explicit symptom. If a specific response is not observed, these should be discontinued. Routine use of nebulized adrenaline, systemic or inhaled corticosteroids leukotriene receptor antagonists and Heliox is not recommended (22, 27). In one study, the use of leukotriene receptor antagonists (montelukast) following RSV bronchiolitis was effective on persistent wheezing (28). In the treatment of infants hospitalized more than 72 hours mucolytic nebulized hypertonic saline treatment was shown to be effective (29). According to AAP (27), hypertonic saline treatment can be recommended for long-term inpatients. Antibiotics are not used. Antibiotics should be used only in cases of secondary bacterial infection (27). In our study, it was found that inhaled bronchodilator treatment is widely used. This may be because prolonged expiration is high in patients with LRTI diagnoses. It was also found that antibiotics are frequently used. One possible reason for this was that the respiratory panel test could not be used in some LRTI inpatients; another reason was that the clinical symptoms of some patients were severe, acute phase reactions were positive, and we could not exclude bacterial infections until the respiratory panel test results were received. In our study, mechanical ventilation treatment was implemented

in two RSV-positive cases who were born at 30-32 gestation weeks. This may indicate that RSV infection progresses more severely in premature infants. Ribavirin is an aerosol virostatic medication that prevents RSV virus protein synthesis, but it is unavailable in our country. AAP does not recommend its routine use because it does not affect mortality, causes toxic damage to the environment, is expensive, is difficult to implement (27). Palivizumab is an anti-RSV monoclonal antibody against RSV is indicated in high-risk infants. Monthly use of Palivizumab in RSV during high season reduces the hospitalization period related to RSV infection.

Palivizumab treatment is recommended in infants born earlier than twenty-nine weeks, in premature with chronic lung diseases, in some congenital heart diseases, in congenital airway disorders, and some neuromuscular diseases (30).

Every year, in the United States of America 91.000 children are hospitalized due to RSV infections, and 300 million dollars are spent on their treatment (31). In a multicenter study in our country, the frequency of hospitalization due to RSV was found to be 13.4 / 1000 under 2 years of age (6). When a cost-benefit analysis of the rapid diagnosis of the causes of viral respiratory tract infections is made, it was identified that the use of rapid tests in diagnosing respiratory tract infections is beneficial in many respects. Rapid diagnosis of viruses prevents unnecessary use of antibiotics and thus prevents the growth of bacteria that are resistant to antibiotics and it shortens the hospitalization period of the patients by leading the patients to appropriate treatment as a result of correct diagnosis (32). The spread of the viruses can be prevented with very simple solutions such as isolating RSV patients in single rooms, designating a certain group of nurses to these patients, washing hands before and after contact with patients, wearing a gown, gloves, and protective masks, and restricting visitors.

Rapid diagnosis of viruses in cases hospitalized in neonatal intensive care units with LRTI diagnosis prevents unnecessary use of antibiotics and thus prevents the growth of bacteria resistant to antibiotics and it shortens the hospitalization period of the patients by leading the patients to appropriate treatment as a result of correct diagnosis.

LIMITATIONS

This was a retrospective study based on medical records. Another limitation of our study is that Respiratory PCR panel examination was not performed using nasopharyngeal swab samples in all of the neonates who were hospitalized with LRTI diagnosis and impaired the ability to gather information about the incidence of RSV and the other viruses.

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