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ORIGINAL ARTICLE

Is it necessary to use antibiotics in infants followed up for transient tachypnea of the newborn?

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ABSTRACT

Objective: Transient tachypnea of the newborn (TTN) is a common cause of respiratory distress in neonates. Despite its benign prognosis, initiating empiric antibiotics is one of the main treatment options besides respiratory support. This study aims to evaluate the use of empiric antibiotics for the treatment of TTN.

Material and Methods: This is a retrospective study of 574 neonates with TTN followed up between January 2015 and 2021. Only 17 neonates (3%) received antibiotics, and they constituted group 1. Group 2 consisted of the remaining 557 (97%) infants who did not receive antibiotics. Demographic and clinical data of the neonates were collected and compared statistically.

Results: There was a statistically significant difference between the groups for tracheal intubation and NICU stay. In group 1, 8 (47%) infants and in group 2, 17 (3.1%) were intubated ($p<0.001$). The mean NICU stay was 7 (5.5–10.5) days in group 1 and 1 (0.8–2.5) day in group 2 ($p<0.001$).

Conclusion: Initiating antibiotic treatment for every neonate diagnosed with TTN is not necessary. Close follow-up of the infant and evidence-based antibiotic use can decrease the adverse effects of antibiotic treatment and the economic burden of this so-called benign disease.

Keywords: Antibiotic treatment, neonate, transient tachypnea of the newborn.

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INTRODUCTION

Transient tachypnea of the newborn (TTN), the most common cause of respiratory distress in neonates, was first described by Avery in 1966 as a condition characterized mainly by tachypnea. It is associated with a reduction in lung compliance due to delayed resorption of alveolar fluid and transient distension of the periarterial spaces.[1] TTN typically appears in late preterm and term infants within the first two hours of life, presenting with tachypnea and signs of respiratory distress, including intercostal retractions, grunting, and flaring of nostrils.[2] The incidence of TTN is 5.7 per 1000 births and can reach up to 35.5 per 1000 births in infants delivered by elective cesarean section (CS) before the onset of labor.[3,4] The main risk factors are elective CS, maternal sedation, maternal diseases such as gestational diabetes and asthma, fetal distress, delivery before 38 weeks' gestational age (GA), low birth weight (BW), and macrosomia.[5]

TTN is generally a self-limiting disorder; however, symptoms may persist for up to 48–72 hours after birth and may last up to 5 days. Until the symptoms resolve, infants may require monitoring and supportive care, such as respiratory support and intravenous fluids, in the neonatal intensive care unit (NICU).[3,5,6] Although the prognosis of TTN is good, associated conditions such as respiratory failure, hypoxemia, or pulmonary air leak syndromes may increase morbidity and prolong hospitalization.[7]

Since the clinical findings are not specific for TTN and are indistinguishable from other respiratory disorders, including surfactant deficiency, pneumonia, sepsis, and meconium aspiration, many NICUs around the world initiate empiric antibiotic treatment for neonates presenting with respiratory distress. However, even short-term unnecessary antibiotic treatment may cause multiple health hazards, such as ototoxicity or nephrotoxicity, alteration of the intestinal microbiota, and the development of drug-resistant organisms and pathogenic yeast in the hospital environment.[8]

Unlike many centers, according to our institution's policy, in the absence of prenatal risk factors for neonatal sepsis or clinical concern for early-onset sepsis, we do not initiate antibiotic treatment for neonates with presumed TTN. The aim of this retrospective study was to assess the management of late preterm (≥34 weeks GA) and term infants with TTN and to evaluate whether empiric antibiotic treatment is required during the management of TTN.

MATERIAL AND METHODS

Study Design

This retrospective study was conducted between January 2015 and January 2021 in two neonatal intensive care units (NICUs) of the same institution. The study was approved by the hospital research and ethical committee (2022.067.IRB1.036) and executed in accordance with the Declaration of Helsinki. There was no funding source relevant to the study.

Study Population

During the study period, a total of 8967 infants were born in both hospitals. Of these, 821 infants with a gestation ≥34 weeks were admitted to the NICU, and 602 of them had an initial diagnosis of TTN. Medical records of these 602 newborns were tracked through the electronic pediatric patient data registry and reviewed. Twenty-eight infants were excluded from the study due to various conditions: bilateral vesicoureteral reflux (n=1), Silver-Russell syndrome (n=1), neonatal seizure (n=2), perinatal asphyxia (n=2), pulmonary hypertension (n=2), neonatal exchange transfusion due to ABO incompatibility and meconium-stained amniotic fluid (n=1), polycystic kidney disease (n=1), and prolonged premature rupture of membranes (n=18).

The remaining 574 infants were enrolled in the study. The infants were divided into two groups based on antibiotic use. Of the 574 infants, 17 (3%) who received antibiotics constituted group 1, while 557 (97%) infants who did not receive antibiotics were named as group 2.

Demographic and clinical information about mothers and neonates was collected, including maternal age, maternal smoking during pregnancy, pregnancy conceived by in vitro fertilization (IVF), gender, birth weight (BW), gestational age (GA), mode of delivery, the need for perinatal resuscitation in the delivery room, insertion of venous lines, the need for continuous positive airway pressure (CPAP), heated humidified high-flow nasal cannula application, intubation, surfactant administration, chest X-ray findings, the development of pneumothorax, oxygen saturation levels (%), highest inspired oxygen fraction (FiO_2) level, duration of antibiotic use, duration of hospitalization, and the mode of feeding.

In all cases, GA was calculated based on the date of the last menstrual period of the mother and/or ultrasound performed in the first trimester of pregnancy. Respiratory distress was defined as a Downes' score >4.[9] Criteria used to define TTN were as follows: documentation of clinical signs of respiratory distress, including tachypnea (respiration rate >60 breaths per minute), intercostal and subcostal retractions, grunting, foaming at the mouth, and flaring of nostrils beginning within the first 30 minutes of life, which were not suggestive of neonatal respiratory distress syndrome, meconium aspiration syndrome, congenital pneumonia, congenital heart disease, or malformations.[6]

Upon admission, all infants were monitored and placed on heated humidified high-flow nasal cannula (Optiflow, Fisher and Paykel Healthcare Limited, Auckland, New Zealand) or CPAP (Sophie, Stephan, Gackenbach) according to the severity of respiratory distress. An air-oxygen blender was used to adjust FiO_2 levels. If a neonate under effective CPAP had persistent or progressive respiratory distress, intubation was performed. After intubation, if FiO_2 was ≥40%, surfactant was administered. Chest X-rays were performed when the clinical course of the patient deviated from the expected course of the disease. Routine blood gas analysis was not performed.

Antibiotic Selection and Initiation

None of the infants received antibiotics upon admission. When the respiratory distress or general condition of the neonate worsened and a possible infection could not be ruled out, antibiotic treatment was initiated after evaluation by an experienced neonatologist in both hospitals. Blood culture samples were collected prior to antibiotic administration. If the infant was intubated, a tracheal aspirate culture was obtained following the intubation procedure. Ampicillin (100 mg/kg/day) and gentamicin (4.5–5 mg/kg every 24–48 hours) were administered for at least 3 days. If the infant's

Table 1: Characteristics of the study population

Characteristics	
Male, n (%)	367 (63.9)
Birthweight (g), (mean±SD)	2941±611
Gestational age (weeks), (mean±SD)	36.9 ±1.8
Late preterm, n (%)	274 (47.7)
Type of labor CS, n (%)	507 (88.3)
Maternal age (years), (mean±SD)	34±5
In vitro fertilization, n (%)	163 (28.4)
Maternal smoking during pregnancy, n (%)	27 (4.8)
Resuscitation in the delivery room, n (%)	240 (41.8)
Heated humidified high flow nasal cannula application, n (%)	159 (27.7)
CPAP, n (%)	415 (72.3)
Intubation, n (%)	25 (4.4)
InSurE, n (%)	22 (88)
Chest X-ray, n (%)	76 (13.2)
Pneumothorax, n (%)	9 (1.6)
Venous lines, n (%)	52 (9.1)
Duration of hospitalization (days), median (25p–75p)	1 (1–3)

CS: Cesarean section; CPAP: Continuous positive airway pressure; InSurE: Intubation surfactant and extubation technique.

clinical symptoms and laboratory tests did not suggest an infection and the cultures were sterile, the antibiotic treatment was discontinued. If the cultures were positive, the antibiotic treatment was adjusted according to the antibiogram results. The duration of treatment was determined based on the infant's condition and lasted a maximum of 7 days.

According to our institution's policy, we do not routinely provide vascular access to neonates with a gestation ≥34 weeks. Instead, we insert an orogastric tube and promote early enteral feeding if there is no contraindication to enteral feeding.

Statistical Analysis

We used SPSS software for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA), for statistical analyses. The variables were investigated using visual (histograms, probability plots) and analytical methods (Shapiro-Wilk test) to determine if they were normally distributed. Descriptive analyses were presented as means±SD for normally distributed variables, as medians (25–75 p) for nonparametric variables, and as percentages for categorical variables. Normally distributed variables were compared using the Student t-test, nonparametric variables using the Mann–Whitney U test, and categorical variables using the chi-square test. A p-value<0.05 was considered statistically significant.

RESULTS

A total of 7916 neonates with a GA of 34 weeks and older were born during the study period. Respiratory problems were observed in 602 infants, meaning respiratory morbidity was observed in 76/1000 neonates. After applying the exclusion criteria, 574 neonates were enrolled in the study. The characteristics of the study population are given in Table 1. The total duration of hospitalization in the NICU ranged between 1 and 3 days. The maximum FiO_2 delivered to the infants during hospitalization was 0.23±0.6 (25 p–75 p=0.21–0.25, range 0.21–0.6).

The characteristics of the groups are demonstrated in Table 2. CPAP was the primary mode of respiratory support for all infants who received antibiotics. All infants receiving antibiotics underwent chest X-ray, whereas 59 (10.6%) infants in group 2 underwent chest X-ray (p<0.001). Of the 9 neonates who developed pneumothorax, 2 (11%) received antibiotics. Of the 25 intubated infants, 22 (88%) received surfactant using the intubation, surfactant administration,

Table 2: Characteristics of the groups

	Received antibiotics Group 1 (n=17)	No antibiotics Group 2 (n=557)	p
Male, n(%)	13 (66.5)	354 (63.6)	0.3
Birthweight (g), (mean±SD)	3047±615	2937±496	0.4
Gestational age (weeks), (mean±SD)	37.2±1.3	36.9±1.8	0.5
CS delivery, n (%)	15 (88.2)	492 (88.3)	0.9
Intubation, n (%)	8 (47.1)	17 (3.1)	<0.001
InSurE, n (%)	7 (41.2)	15 (2.7)	<0.001
Chest X-ray, n (%)	17 (100)	59 (10.6)	<0.001
Pneumothorax, n (%)	2 (11.8)	7 (1.3)	0.026
NICU stay (days), median (25p–75p)	7 (5.5–10.5)	1 (1–2.5)	<0.001

SD: Standard deviation; CS: Cesarean section; InSurE: Intubation surfactant and extubation technique; NICU: Neonatal intensive care unit.

and extubation (InSurE) technique. Antibiotics were initiated in 7 (31.8%) of these 22 babies. None of the mothers of infants who received antibiotics smoked.

The duration of hospitalization was longer in infants who received antibiotics (Table 2). Infants with lower GA stayed in the NICU longer, and this relationship was statistically significant (r=-0.4, p<0.001). The duration of antibiotic therapy ranged between 3 and 7 days. Eight infants received antibiotics for 5 to 7 days, while the others received antibiotics for only 3 days. Only one infant had culture positivity, with E. coli isolated from the tracheal aspirate culture; there was no need to change antibiotics. There was no growth in hemocultures. None of the infants experienced morbidity or mortality.

DISCUSSION

Despite its benign prognosis, TTN may increase the need for respiratory support and invasive procedures, prolong NICU stay, and cause maternal-infant separation, parental anxiety, and adverse effects on the successful establishment of breastfeeding. For treatment, in addition to supportive therapy, the main practice is to initiate antibiotics since the clinical signs are not specific for this condition, and those nonspecific signs may herald other, more serious respiratory diseases.[8–12] On the other hand, the use of unnecessary antibiotics in neonates is associated with organ toxicity, increased antibiotic resistance patterns, and alteration of the intestinal microbiota.[8] Moreover, early-life antibiotic use has been linked to allergy, asthma, atopic disease, food allergy, childhood obesity, and type 1 diabetes due to alteration of the gut microbiome.[13–15] In this retrospective study, we demonstrated that the use of antibiotics was higher in infants diagnosed with TTN with an atypical, complicated, or severe course. Therefore, we consider that empiric antibiotics are not essential for the treatment of TTN unless the course deviates from the expected disease progression.

TTN, also known as retained fetal lung fluid syndrome, is a common cause of early respiratory distress in neonates. It presents with tachypnea and increased work of breathing in late preterm and term infants, persisting for 24 to 72 hours. In utero, fetal lungs produce lung fluid, which is critical for normal lung growth and development. The air sacs and airspaces are filled with this fluid. From the onset of labor to delivery of a term neonate, approximately 100 ml of lung fluid must be cleared for effective gas exchange to occur. Late in gestation and before birth, the main mechanism for fluid removal from the lungs is sodium uptake across the lung epithelium via liquid reabsorption. Glucocorticoids and thyroid hormones activate sodium channels for this absorption. This mechanism is enhanced by labor. Therefore, delivery before labor onset—meaning the absence of stress or hormonal influences of labor—results in fetal lung fluid retention.[12,16] Consequently, it has been suggested that to prevent TTN, the ideal approach is to reduce the incidence of elective CS before 39 weeks of GA.[17]

Ahimbisibwe et al.[18] reported that the risk of respiratory morbidity was significantly higher following elective CS<39 GA. Similarly, Zanardo et al.[19] demonstrated that infants born by elective CS at term are at higher risk for respiratory disorders than those born by vaginal delivery. Many et al.[20] conducted a study with 588 pregnant women at term and found that neonates delivered by elective CS had a significantly higher rate of respiratory morbidity compared to those delivered vaginally. According to the results of a multicenter study in Türkiye, the overall CS rate was 51.2%. In public, private, and university hospitals, the rates were 39.7%, 70.6%, and 70.3%, respectively.[21]

In our center, similar to the results of Turkish national data, CS deliveries outnumbered vaginal deliveries, with a rate of 88.3%, which was the most important risk factor for the development of TTN. We think that the main reason for the high CS rates in our center is that it is a tertiary university hospital where high-risk pregnancies are frequently followed up. The incidence of TTN has been reported to be 5.7 per 1000 births in late preterm and term infants and can reach up to 35.5 per 1000 births in term infants delivered by elective CS before labor onset.[3,4] In our study, the incidence of neonatal respiratory morbidity was 76 per 1000 births, which was much higher than reported in the literature. This high incidence of respiratory morbidity in our population may be due to the high rates of late preterm delivery and CS.

Delivery by CS increases the risk of respiratory morbidity, particularly if performed before the onset of labor. Morrison et al.[4] showed that the incidence of respiratory morbidity was 35.3 per 1000 in term neonates delivered by CS before labor onset, 12.2 per 1000 in term neonates delivered by CS during labor, and 5.3 per 1000 in vaginally delivered term neonates. Ahimbisibwe and colleagues demonstrated that the incidence of neonatal respiratory morbidity was 37 per 1000 elective CS births in neonates with a GA of 36 weeks and above.[18] Unfortunately, we do not have data on whether the CS deliveries in our study were elective or performed during labor.

To distinguish TTN from congenital pneumonia and/or sepsis may be a challenge. Therefore, many neonates hospitalized in the NICU due to TTN receive antibiotics.[7,20] Salama et al.[22] conducted a study with 168 neonates diagnosed with TTN; of these, 106 (63%) received antibiotics and 62 (37%) did not. They found that two infants in the treated group and one infant in the non-treated group had microbiologically confirmed bacteremia. They concluded that, with close observation in the NICU, the empiric use of antibiotics may be avoidable.

Similarly, Weintraub et al.[8] reported that of 745 infants with TTN, 251 (33.7%) received antibiotics. They noted that in the absence of infectious risk factors, empiric antibiotic treatment may not be warranted for late preterm and term infants with TTN. Dehdashtian et al.[3] assessed the clinical course of 130 neonates diagnosed with TTN. Of these, 65 received antibiotics while 65 did not. They concluded that infants with TTN without prenatal risk factors and with a negative CRP do not need to be administered antibiotics. In our study, of the 574 neonates admitted to the NICU, only 17 (3%) received antibiotics, which was lower than in previous studies, and moreover, none of them experienced severe morbidity or mortality.

It is recommended to initiate empiric antibiotic coverage in all neonates presenting with respiratory distress, although this practice is not evidence-based.[10,11] The gold standard for the definitive diagnosis of neonatal sepsis is to isolate the offending pathogen from a blood culture.[23,24] Conventionally, before antibiotics are initiated, blood cultures should be obtained, and the infants should be treated until the blood culture results become negative.[1] In the literature, the positive rate of neonatal blood cultures has been reported as 25–54%.[10,25,26] On the other hand, blood cultures are less sensitive, time-consuming, and therefore not suitable for early detection of infection.

Furthermore, even for a short period, antibiotics may have adverse effects on normal flora colonization, may promote drug-resistant strains in the NICU population, and may encourage pathogenic yeast growth in patients and the NICU environment.[27,28] In addition to these severe adverse effects, using antibiotics for the management of TTN increases the duration of hospitalization and causes an economic burden.

Dehdashtian et al.[3] reported that the mean duration of antibiotic administration and hospitalization was 7 days, which was higher than in those who did not receive antibiotics (5 days). Salama et al.[22] showed that the mean hospital stay was 72±6 hours for infants receiving antibiotics and 48±3 hours for those not receiving antibiotics. Kasap et al.[7] conducted a study with 95 neonates with TTN, all of whom received antibiotics. The mean duration of antibiotic treatment was 4.6±2.3 days, and the duration of hospitalization was 137.1±95.8 hours.

Costa et al.[29] conducted a retrospective study of neonates with respiratory distress. Twenty-nine newborns were diagnosed with pneumonia and required antibiotics, whereas 202 were diagnosed with TTN and did not require antibiotics. The duration of NICU stay was 10 (7–24) days for pneumonia and 3 (1–17) days for TTN, which was statistically significant.

Similar to the literature, in our study, infants who received antibiotics stayed in the NICU longer than those who did not. For infants receiving antibiotics, the median NICU stay was 7 (5.5–10.5) days, whereas it was 1 (1–2.5) day for infants not receiving antibiotics.

Although TTN is known to be a self-limiting and benign disorder, there have been cases resulting in respiratory failure and death. Malignant TTN describes severe respiratory morbidity and subsequent mortality due to persistent pulmonary hypertension of the newborn, which occurs in neonates delivered by elective CS.[30] TTN may cause severe morbidities due to hypoxia, pulmonary air leak syndromes, or respiratory distress.[7] In the present study, 72.3% of infants received CPAP, and 25 (4.4%) were intubated. All infants who received antibiotics had CPAP as the primary mode of ventilation, and 47.1% of them were intubated. Based on these statistical findings, we speculate that antibiotic therapy can be reserved for infants whose clinical courses are more severe or complicated. Additionally, in the present study, none of the babies experienced severe morbidity or died.

When a neonate is admitted to the NICU, depending on the severity of illness, numerous interventions and medications are applied.[31] However, every intervention may lead to complications. Therefore, utility and futility should be the cornerstone of every medical decision. For instance, nosocomial sepsis is a major problem in NICUs, particularly in developing countries. The routes of infection are varied, and most are preventable. Intravenous lines are an important cause of morbidity and mortality, with the cannula hub serving as a major portal of entry for sepsis-causing agents.[32] As a policy in our unit, we do not insert venous lines for every infant hospitalized in the NICU for TTN. In the present study, of the 574 neonates, 52 (9.1%) had venous lines for antibiotic or intravenous fluid treatment.

Although our center is a government-supported NICU, every intervention and prolonged stay imposes a significant financial burden. The cost of NICU stay is approximately 125–170$ per day in Türkiye; however, in some cases, this cost may be exceeded, causing a serious economic burden on the hospital. In the present study, all infants treated with antibiotics (n=17) underwent chest X-ray, whereas 59 (10.6%) infants who did not receive antibiotics had a chest X-ray. Although exposure to high doses of radiation may affect vulnerable tissues (thyroid, gonads, and brain), the recommended safe level of radiation exposure is not well established.[33] Apart from the harm of ionizing radiation, the financial burden is another important issue. In our center, the cost of a chest X-ray is 47$ per patient. Principally, we do not perform chest X-rays on every neonate with respiratory distress. In this study, 76 (13.2%) infants underwent chest X-ray. This suggests that instead of performing routine chest X-rays, conducting them only when the clinical course deviates from the expected trajectory is more reasonable.

In our opinion, rather than applying a standard approach to neonates with TTN, a patient-centered approach is more rational. It is more beneficial to the patient and significantly reduces hospital costs. We believe that minimum handling and maximum observation should be the main policy for every hospitalized infant.

Limitations

This study has some limitations. The main limitation was its retrospective design, including neonates in two NICUs of the same institution. However, due to the consistent policy and quality of patient care in our institution, we believe this did not affect our results. Furthermore, due to the retrospective design, we could not categorize CS deliveries as elective or during labor. Another limitation was that we did not review maternal risk factors such as diabetes or asthma. The final limitation was the low number of infants who received antibiotics.

CONCLUSION

According to our results, we suggest a more conservative approach to antibiotic use in hospitalized infants with TTN. In our opinion, the ideal approach for the management of TTN is to closely follow up the neonate in the NICU, provide vigilant medical support, and use evidence-based antibiotic treatment. This approach will help reduce unnecessary antibiotic use and shorten the duration of hospitalization. In this way, both the adverse effects of antibiotic use will be prevented, and the economic burden of this so-called benign disease will be significantly diminished.

Statement

Ethics Committee Approval: The Koç University Ethics Committee granted approval for this study (date: 16.02.2022, number: 2022.067.IRB1.036).

Author Contributions: Concept – SE, TG; Design – SE, YC, TG; Supervision – TG; Materials – SE, KK; Data Collection and/or Processing – SE, KK; Analysis and/or Interpretation – TG, YC; Literature Search – YC; Writing – YC, TG; Critical Reviews – TG.

Conflict of Interest: The authors have no conflict of interest to declare.

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