

Research Article

Epidemiology and Susceptibility Patterns of Hospital-Acquired Conjunctivitis in a Neonatal Intensive Care Unit

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Abstract

Objectives: The aims of this study were to determine the prevalence of pathogens causing bacterial hospital-acquired conjunctivitis (HAC) and to provide information about antibiotic susceptibility patterns among inpatient infants.

Methods: Infants with gram-negative (Group 1) or -positive (Group 2) bacterial conjunctivitis were included. Of 365 patients, 98 tested positive for bacteria; all data were collected retrospectively. Isolated pathogens and antibiotic susceptibility patterns were also obtained from the patient records.

Results: The most common pathogens were gram-negative bacteria, found in Group 1 (n=80, 82%). Group 2 included 18 (18%) infants with gram-positive conjunctivitis. There were no significant differences in demographics or clinical characteristics between the two groups. Ten neonates in Group 1 (12.5%) and two neonates in Group 2 (11.1%) had concomitant sepsis (p=0.60). In gram-positive conjunctivitis cases, *Staphylococcus aureus* (50%) was the predominant pathogen. In gram-negative conjunctivitis cases, *Pseudomonas species* (46.2%) was the most common pathogen, followed by *Klebsiella species* (27.5%) and *Escherichia coli* (12.5%). In gram-negative bacteria, the antibiotic resistance rates to gentamicin, netilmicin, and second- and third-generation fluoroquinolones were 48.1%, 14.3%, and 13% and 8.6%, respectively. We did not observe any unresponsive or complicated conjunctivitis cases.

Conclusion: Surveillance is essential in determining the rate of HAC and identifying the factors associated with the infection, and it is important to plan and evaluate prevention strategies.

Keywords: Conjunctivitis, hospital-acquired, neonatal intensive care unit, neonate

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Nosocomial infections are common in pediatric wards and represent one of the major causes of morbidity in neonatal intensive care units (NICUs).^[1] Hospital-acquired conjunctivitis (HAC) is one of the most common nosocomial infections encountered in NICUs, affecting 1.6%–12% of all newborns.^[2, 3] The signs and symptoms of conjunctivitis are similar across different etiologies.

Preterm infants are at particularly high risk for HAC owing to the severity of the illness and exposure to invasive me-

chanical devices and resistant microorganisms.^[4, 5] Other risk factors for HAC that have been identified include development of retinopathy of prematurity (ROP), occurrence of nasolacrimal secretions due to mechanical ventilation, and oxygen delivery by nasal cannula.^[6, 7] A presumptive diagnosis can be made based on Gram stain results; however, the definitive diagnosis should be made based on conjunctival culture results. Gram-negative conjunctivitis can lead to complications that are more serious than other bacterial conjunctivitis.^[3]

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The objectives of this study were to determine the prevalence of the bacterial pathogens that cause bacterial HAC and to provide information about antibiotic resistance patterns, particularly of gram-negative pathogens, among inpatient preterm infants.

Materials and Methods

Study Design and Population

This retrospective study was conducted in a busy NICU at Dr. Zekai Tahir Burak Women's Health Training and Research Hospital, Ankara, Turkey, between January 2010 and December 2013. This trial was approved by the local ethics committee. Infants with culture-proven conjunctivitis were enrolled in the study. Infants were excluded if they had any obvious ocular malformations or if two or more bacteria were isolated from the same sample. The patients were categorized into two groups: Group 1 (gram-negative conjunctivitis) and Group 2 (gram-positive conjunctivitis). The patient data, which were collected retrospectively, consisted of demographic characteristics (gestational age and birth weight), birth history (type of birth and multiple births), length of stay in the NICU, device utilization (mechanical days of intubation or continuous positive airway

pressure and phototherapy), sepsis, and short-term clinical outcomes. In our NICU, retinal screening examinations for ROP were conducted in accordance with American Academy of Pediatrics policies.^[8] The first eye examinations were performed by ophthalmologists at a postnatal age of 4–6 weeks.

Definition of HAC and Intervention of Neonatal Conjunctivitis

Newborns admitted to NICU who were diagnosed with conjunctivitis within 48 h of life were excluded from the study. HAC cases were considered eligible if they met the diagnostic criteria (for specific types of infections in the acute care setting) of the Centers for Disease Control and Prevention/National Healthcare Safety Network surveillance definition.^[9] Patients were examined several times until they achieved complete recovery.

We used povidone-iodine (PVP-I) prophylactically to prevent neonatal conjunctivitis after each delivery. We prepared 2.5% PVP-I by diluting 10% PVP-I with sterile distilled water under sterile conditions.^[10]

Microbiological Procedures

After clinical conjunctivitis was detected, eye cultures were

Table 1. Demographic and clinical characteristics of the study infants

Characteristics	Group 1 (n=80) (Gram-negative)	Group 2 (n=18) (Gram-positive)	P
Maternal age, (years) ^a	27.9±5.9	29.5±6.2	0.28
Premature prolonged rupture of membranes ^b	17 (21)	2 (11)	0.51
Meconium-stained amniotic fluid ^b	4 (5)	0 (0)	0.44
Antenatal steroid ^b	38 (47.5)	6 (33)	0.31
Cesarean Section ^b	69 (86)	13 (72)	0.16
Gestational age (weeks) ^a	30.7±4.2	32.2±4.6	0.20
Birth weight (g) ^a	1362±918	1451±768	0.70
Male ^a	41 (51.2)	12 (66.7)	0.18
APGAR score 5 min. ^c	8 (4–10)	8 (5–9)	0.88
Mechanical ventilation (days) ^c	6 (1–58)	2 (1–5)	0.11
Continuous positive airway pressure (days) ^c	4 (1–100)	2 (1–18)	0.30
Oxygen delivery (days) ^c	5 (1–120)	4.5 (1–47)	0.63
Phototherapy ^b	64 (80)	16 (88.9)	0.51
Grade 3-4 Intraventricular hemorrhage ^b	7 (8.7)	3 (16.7)	0.15
Retinopathy of prematurity (photocoagulation required) ^b	9 (11.2)	0 (0)	0.69
Chronic lung disease ^b	9 (11.2)	0 (0)	0.69
Concomitant sepsis ^b	10 (12.5)	2 (11.1)	0.60
Conjunctivitis (day of presentation) ^c	8 (4–71)	8.5 (4–58)	0.48
Mortality ^b	10 (12.5)	1 (5.6)	0.68
Length of hospital stay (days) ^a	50.3±38.4	37.4±31.6	0.19

^a: Values are given as mean ± standard deviation; ^b: values are given as percentage; ^c: values are given as median (min–max); PDA: patent ductus arteriosus.

Table 2. Gram positive and negative pathogens among infants according to the birthweight

	<1500 g (n=59)	≥1500 g (n=39)
Gram-positive		
<i>Staphylococcus aureus</i>	5 (8.5)	4 (10.3)
<i>Staphylococcus epidermidis</i>	4 (6.8)	4 (10.3)
<i>Enterobacter cloaca</i>	2 (3.4)	1 (2.6)
<i>Enterococcus faecalis</i>	1 (1.7)	0 (0)
<i>Staphylococcus capitis</i>	1 (1.7)	0 (0)
<i>Enterobacter aerogenes</i>	1 (1.7)	0 (0)
Gram-negative		
<i>Pseudomonas aeruginosa</i>	19 (32.2)	17 (43.6)
<i>Klebsiella pneumoniae</i>	15 (25.4)	4 (10.3)
<i>E. coli</i>	3 (5.1)	6 (15.4)
<i>Serratia marcescens</i>	4 (6.8)	0 (0)
<i>Klebsiella oxytoca</i>	2 (3.4)	1 (2.6)
<i>Pseudomonas putida</i>	1 (1.7)	0 (0)
<i>Acinetobacter baumannii</i>	1 (1.7)	2 (5.1)

collected immediately by members of the nursing staff, and the infants were treated locally with antibiotic drops (tobramycin and netilmicin) and ointments. Treatment was arranged in accordance with the susceptibility testing and clinical responses. Swab cultures were sent to the laboratory in sterile vials with a stopper. They were then immediately cultured on tryptic soy agar with 5% sheep blood, chocolate, and eosin–methylene blue lactose sucrose agar plates (Becton Dickinson, Sparks, MD). The plates were incubated in an aerobic environment with 5% CO₂ at 35°C and were examined daily for a minimum of 48 h until the culture was negative. Gram-stained smears were also prepared for preliminary examination. Antimicrobial susceptibility testing was performed in accordance with the Clinical and Laboratory Standards Institute guidelines by either Vitek 2 (bioMérieux, Lyon, France) or the conventional agar disk diffusion method.^[11] The cultures were not routinely tested for viral pathogens or chlamydia. Clinical diagnosis of adenoviral infection was made based on pathognomonic symptoms. No surveillance cultures were obtained for this study population.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows version 17.0 (SPSS Inc, Chicago, IL). Data were presented as mean±standard deviation or range in continuous variables and as median in categorical variables. Comparisons between groups for categorical variables were conducted using the chi-square test and were given as numbers and total percentages. A p value <0.05 was considered to be statistically significant.

Table 3. Antibiotic resistance in Gram-negative conjunctivitis*

Antibiotics	No. of Isolates	%
Ampicillin/Sulbactam	23/33	69.7
Cefazolin	24/35	68.6
Cefotaxime	24/35	68.6
Ceftriaxone	25/37	67.6
Gentamicin	37/77	48.1
Tetracycline	5/13	38.5
Cefepime	28/77	36.4
Trimethoprim/sulfamethoxazole	9/30	30
Ceftazidime	21/76	27.6
Cefoxitin	10/37	27
Aztreonam	19/73	26
Imipenem	13/77	16.9
Netilmicin	2/14	14.3
Ciprofloxacin	10/77	13
Piperacillin/tazobactam	6/68	8.8
Ertapenem	2/23	8.7
Levofloxacin	6/70	8.6
Amikacin	4/68	5.9
Meropenem	4/68	5.9

*Not all organisms had documented susceptibilities.

Results

Over a period of 3 years, 365 conjunctival swab cultures were performed, of which 98 (26.8%) were positive. HAC occurred in 7.2% of all hospitalized infants during this study period. The most common pathogens detected on the conjunctival swab cultures were gram-negative bacteria (Group 1, n=80,82%). Group 2 included 18 (18%) infants with gram-positive conjunctivitis. The median ages of the two groups were similar: Group 1, 8 (range, 4–71) days and Group 2, 8.5 (range, 4–58) days (Table 1). Bilateral conjunctivitis was present in 36.8% of the infants, and unilateral involvement was present in 63.2% of the infants.

The demographic and clinical characteristics of the infants are summarized in Table 1. There were no significant differences between the groups in terms of these characteristics. Ten neonates in Group 1 (12.5%) and two neonates in Group 2 (11.1%) had proven concomitant sepsis (p=0.60). We did not observe any unresponsive or complicated conjunctivitis cases.

All the isolated bacteria accountable for conjunctivitis in the enrolled infants are listed in Table 2. Of the gram-positive organisms, *Staphylococcus aureus* (50%) was more predominant than *S. epidermidis* (44.4%). The most common gram-negative pathogens were, in order of frequency, *Pseudomonas species* (46.2%), *Klebsiella species* (27.5%), *Escherichia coli* (12.5%), *Serratia marcescens* (5%), *Enterobacter species* (5%), and *Acinetobacter baumannii* (3.8%).

The antibiotic susceptibility patterns of the gram-negative organisms are listed in Table 3. The gram-negative organisms showed the least susceptibility to ampicillin/sulbactam, cefazolin, cefotaxime, and ceftriaxone, with antibiotic resistance rates of 69.7%, 68.6%, 68.6%, and 67.6%, respectively. The percentage of organisms resistant to gentamicin, netilmicin, and second- and third-generation fluoroquinolones (ciprofloxacin and levofloxacin) were 48.1%, 14.3%, and 8.6% and 13%, respectively. The gram-positive organisms were the least susceptible to ampicillin and penicillin, with antibiotic resistance in 93.3% and 100% of the patients, respectively. Three infants were diagnosed with gram-negative conjunctivitis after routine retinopathy examinations. Two of the isolated organisms were *Klebsiella species*, and the other organism diagnosed was *Pseudomonas species*.

There was no statistically significant difference in incidence of gram-negative conjunctivitis between infants with birth weights less than and above 1500g (78.9% and 83.3, respectively; $p=0.6$). Gram-positive conjunctivitis rates were also similar in infants with birth weights less than and above 1500g (21.1% and 16.7%, respectively). The results of this study indicate that the cause of gram-negative conjunctival infection is not associated with low birth weight (<1500 g).

Discussion

There are different definitions of HAC in the current literature. In the present study, HAC was defined as conjunctivitis that occurred 48 h or more after admission and that was not related to maternal infection.^[6] There are only a few studies on HAC in the NICU setting. This trial was one of the largest studies conducted recently to examine HAC in a single center. HAC affected 7.2% of ill neonates in this study, consistent with other reports in which HAC rates ranged from 6% to 18% of neonates.^[6, 7-12, 13]

Chen et al.^[13] reported in their study that gram-negative conjunctivitis affecting 25 (38%) patients accounted for 35 (25%) bacterial isolates. These 35 gram-negative isolates included *Klebsiella species* (23%), *E. coli* (17%), *Serratia species* (17%), and *Haemophilus influenzae* (17%). These data conflict with results obtained from the general pediatric population, which suggest that *H. influenzae* is the leading gram-negative pathogen in pediatric conjunctivitis.^[14,15] In the same study, it was suggested that gram-negative conjunctivitis had a significant relationship with low birth weight and low gestational age. The authors reported that infants weighing less than 1500 g at birth were 4.35 times more likely to develop gram-negative conjunctivitis compared with other infections. According to the same study,

except for a case of culture-positive ocular infection, all of the infected infants' weights were <1500g. However, in the current study, we found no statistically significant difference between birth weights ≤ 1.500 g and > 1.500 g in terms of gram-negative pathogen as a causative agent.

The results of our study showed that the prominent microorganisms were *Pseudomonas species*, *Klebsiella species*, and *E. coli*. Contrary to the previous literature, a higher rate of *Pseudomonas species* was isolated. The variation in the frequency of isolated microorganisms in this study might be attributed to our different hospital environment. The most important advantage of our study is that the population was relatively large compared with that of other studies in the literature. In addition, we demonstrated a resistance pattern to drugs; therefore, these results can serve as a guide to the use of empirical antibiotics until culture results are determined.

In our study, 54% of the neonates were male. There was no significant relationship with respect to sex, which is agreement with other similar studies.^[6, 16] In the second part of the study, antibiotic susceptibility was tested. Resistance to β -lactam antibiotics was the highest, with ampicillin/sulbactam, cefazolin, and cefotaxime resistance rates of 69.7%, 68.6%, and 68.6%, respectively. This resistance pattern should be taken into consideration when determining the choice of treatment because improper empiric antibiotic treatment is common and can result in increased mortality in critically ill premature infants. The empiric antibiotic regimen should be reassessed and personalized immediately after culture and susceptibility results are obtained. We found a good response to netilmicin sulfate 0.3% eye drops (as opposed to gentamicin sulfate 0.3% eye drops) for initial empirical antibiotic usage, which we strongly recommend due to antimicrobial resistance patterns. An underdeveloped immune system, common in premature infants, could make this population vulnerable to a local ocular infection becoming a systemic infection; therefore, early appropriate usage of empirical therapy is essential. With strict attention to infection control practices and a relevant benchmark for comparison, interventions to decrease conjunctivitis in this vulnerable population can be implemented and assessed successfully.

Topical levofloxacin and ciprofloxacin have proven to be effective against bacterial conjunctivitis.^[17, 18] The resistance rates to second- and third-generation fluoroquinolones (ciprofloxacin and levofloxacin) were found to be 8.6 and 13%, respectively; we did not use these topical antibiotics to treat HAC. Surveillance is essential in determining the rate of HAC and identifying the factors associated with the infection, and it is important to plan and evaluate preven-

tion strategies. Birth weight and gestational age are clinically significant risk factors associated with gram-negative conjunctivitis in the NICU setting, as shown in previous studies.

Our study has a number of limitations such as its retrospective design and the fact that it was conducted in a single institution. Another limitation is that it did not reveal any no-growth conjunctival cultures that might be attributed to other organisms such as anaerobes or viruses.

There is variation in frequency of infections, spectrum of potential pathogens, and antimicrobial susceptibility patterns among different NICUs. HAC should not be underestimated, and empiric antibiotic selections should be based on local susceptibility patterns of microorganisms at each clinic. Therefore, it is essential to select appropriate early empirical therapy when treating premature infants; in addition, usage requirements might change. Information regarding which infants should receive eye cultures is not available in the literature; thus, further studies are required for clarification as well as to study cost-effectiveness prospectively.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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