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Multi-resistant viridans streptococcal pneumonia and sepsis in the ventilated newborn

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Summary Mechanical ventilation increases the frequency of nosocomial infections. This study describes the frequency of multi-resistant viridans streptococcal colonisation, the clinical course of nosocomial sepsis and ventilator-associated pneumonia in mechanically ventilated neonates in the neonatal intensive care unit of Ankara University Hospital. Seventy-nine ventilated newborns were enrolled. Broncho-alveolar lavage culture and blood cultures were positive in 44 (56%) and 17 (22%) patients, respectively. The most predominant micro-organisms in broncho-alveolar lavage cultures were multi-resistant viridans streptococci (29, 66%). Viridans streptococci were also one of the predominant organisms in blood cultures (5/17, 29%). In 29 patients with broncho-alveolar lavage positive for viridans streptococci, nine (31%) had colonisation, 15 (52%) had ventilator-associated pneumonia and five (17%) had sepsis owing to viridans streptococcus. Ventilator-associated pneumonia was encountered in 52/1000 ventilation days. Mortality was caused by infection in three (10%) of them. Mechanically ventilated neonates in our neonatal intensive care unit had a high rate of both multi-resistant viridans streptococcus airway colonisation and subsequent ventilator-associated pneumonia and sepsis.

Introduction

Improved medical care of high-risk newborns in recent decades has resulted in better survival of neonates in intensive care units (NICU), particularly very low birthweight (VLBW) infants. It has been accompanied, however, by an increase in invasive procedures including assisted ventilation. These infants are at risk of bacteraemia owing to their compromised immune status, frequent exposure to invasive diagnostic procedures and potentially harmful therapeutic regimens. Mechanical ventilation increases the risk of airway colonisation, ventilator-associated pneumonia (VAP) and nosocomial sepsis.[1–3]

Several risk factors have been associated with the development of nosocomial infections.[1,4–7] Evidence suggests that the incidence of nosocomial infection caused by multi-resistant bacteria might be related to an imbalance of the resident bacterial flora. Previous use of antibiotics has been largely blamed as a risk factor for colonisation by multi-resistant bacteria.[1]

Viridans streptococci are usually commensal in the mouth and harmless but can cause sepsis in neonates and immunocompromised individuals and have emerged as a significant cause of septicaemia and VAP in neonates.[8–10]

The aim of the present study was first to determine multi-resistant *Streptococcus viridans* colonisation rates and the clinical course of neonatal sepsis and VAP during a 2-year period in a tertiary neonatal intensive care unit in Turkey.

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Subjects and Methods

This retrospective study was conducted in the NICU of Ankara University Hospital between January 2000 and December 2001. During this period, 700 newborns were admitted to this 25-bed, tertiary care unit. A total of 79 infants were mechanically ventilated and investigated for tracheal colonisation, VAP and nosocomial sepsis.

Information was recorded on gestational age, birthweight, mode of delivery, gender, reason for ventilation, previous antibiotics, age at onset of ventilation, duration of ventilation and hospitalisation, organisms isolated in blood and broncho-alveolar lavage cultures, proven nosocomial sepsis, pneumonia, bronchopulmonary dysplasia (BPD), outcome and mortality owing to infection. Data were collected from the computer-based patient records.

Gestational age was defined according to the mother's last menstrual period and/or the New Ballard scoring system. Preterm delivery was defined as any child born before 38 weeks gestation and VLBW as birthweight <1500 g. BPD was defined according to the need for treatment with oxygen at 36 weeks gestation.[11] NNIS definitions were used for nosocomial infections. Proven nosocomial sepsis was defined as a positive blood culture with infection not present or incubating at the time of admission to the NICU, with onset at least 48 hours after admission.[12–14] VAP was diagnosed when a patient developed new and persistent radiographic evidence of focal infiltrates $\geqslant 48$ hours after initiating mechanical ventilation.[15,16] Device-associated infection rates were calculated by dividing the number of device-associated infections ($\times 1000$) by the total number of appropriate device-days.[12] Airway colonisation was defined by presence of an identified organism in two or more broncho-alveolar lavage (BAL) cultures in an infant without clinical or bacteriological evidence of systemic or local infection.[16]

Blood and BAL cultures, chest radiographs and blood samples for complete blood count (CBC), micro-sedimentation and C-reactive protein were obtained from all infants with respiratory failure before ventilation for diagnosis of infection. Blood and BAL cultures were obtained according to methods previously reported.[2] A white cell count either <5000 or $>20000/mm^3$, an immature total neutrophils ratio >0.2, C-reactive protein level >1 mg/dl and micro-sedimentation level above the normal rate (by adding three to the age of the newborn in days, beyond 2 weeks of life more than 20 mm/per hour) were accepted as positive laboratory signs of infection. Two or more positive laboratory signs strongly suggested sepsis.[17] Thereafter, blood and BAL cultures were taken almost daily, and chest radiographs and blood samples for CBC, C-reactive protein and micro-sedimentation were obtained following clinical guidelines. Cerebrospinal fluid and urine culture were taken if nosocomial sepsis was suspected. For early microbiological detection, analyses were done with a BACTEC fluorometric detection system. The threshold number of organisms for infection were $>10^4$ colony-forming unit/ml in BAL culture.[18] Micro-organisms were identified by conventional methods and antibiotic susceptibilities determined using the disc diffusion method and measurement of minimum inhibitory concentrations according to NCCLS guidelines.[19]

In the case of early onset sepsis, neonatal pneumonia or meconium aspiration, the patient was started empirically on ampicillin and netilmicin on admission. Patients diagnosed with late-onset nosocomial sepsis before the start of ventilation and who died within the 1st 48 hours of ventilation were excluded from the study. Patients with oxygen dependency who died before completing 36 weeks gestation were not included as patients with BPD.

Data were collected on standardised forms and analysed using SPSS version 9 for Windows. Data are reported as frequencies or means with standard deviations (SD).

TABLE 1. *Clinical characteristics of ventilated neonates [mean (SD) unless specified].*

Characteristic	Total (%) $n=79$
Birthweight (g)	1957 (992), median 1680
Gestational age (w)	33 (4.4)
Prematurity (%)	60 (76)
Male (%)	47 (60)
Caesarean section (%)	49 (62)
Age at onset of ventilation (d)	2.3 (3.7)
Duration of Ventilation (d)	7.4 (8.4)
Duration of Hospitalisation (d)	28.4 (24.9)
Previous antibiotic Administration (%)	35 (44.3)
Day of ventilation at Microbiological identification	4.8 (3.1)

TABLE 2. *Reasons for mechanical ventilation.*

	Total (%) $n=79$
Respiratory distress	25 (32)
Transient tachypnoea	12 (15)
Congenital cardiac anomalies	9 (11)
Neonatal pneumonia	7 (9)
Early onset sepsis	6 (8)
Necrotising enterocolitis	4 (5)
Meconium aspiration pneumonia	5 (6)
Perinathal asphyxia	5 (6)
Hydrops fetalis	3 (4)
Apnoea	2 (3)
Aspiration pneumonia	1 (1)

Results

Seventy-nine newborns were enrolled in the study. The mean (SD) birthweight and gestational age of the study group were 1957 (992) g and 32.6 (4.4) weeks. The patients' characteristics are described in Table 1 and the reasons for mechanical ventilation in Table 2. Positive BAL and blood cultures were obtained from 44 (56%) and 17 (22%) patients, respectively. The distribution of pathogens identified is shown in Table 3. Some patients had more than one infection during hospitalisation. Seventeen patients with positive blood cultures were examined for meningitis but their cerebrospinal fluids were sterile.

The predominant micro-organism in the BAL and blood cultures was multi-resistant viridans streptococci (29/44, 66% and 5/17, 29%, respectively). Blood isolates of viridans streptococci were identified as *Streptococcus mitis* by the API identification system. Antibiotic susceptibility patterns of *S. mitis* and viridans streptococci isolated from the blood and BAL cultures were similar. Viridans streptococci were identified in the BAL culture 2–5 days before the blood culture became positive for the same micro-organism in all of the cases of sepsis.

Nine (31%) of the 29 patients with BAL cultures positive for viridans streptococci

TABLE 3. *Distribution of pathogens in ventilated newborns.*

	BAL culture positive $n=44/79$ (%)	Blood culturepositive $n=17/79$ (%)
Gram-positive	40 (91)	8 (47)
Viridans streptococci	29 (66)	5 (29)
Staphylococcus epidermidis	8 (18)	3 (18)
Enterococcus	3 (7)	0
Gram-negative	42 (95)	12 (70)
Klebsiella pneumoniae	27 (61)	5 (29)
Escherichia coli	4 (9)	1 (6)
Pseudomonas aeruginosa	3 (7)	1 (6)
Acinetobacter baumannii	3 (7)	2 (12)
Stenotrophomonas maltophilia	2 (5)	2 (12)
Serratia marcescens	3 (7)	1 (6)
Fungus		
Candida albicans	5 (11)	2 (12)
Multiple pathogens	17 (39)	3 (18)

had colonisation, 15 (52%) had VAP and five (17%) had viridans streptococcal sepsis. VAP was encountered on 52/1000 ventilation days. Five patients (17%) with BAL positive for viridans streptococci died and death was caused by infection in three (10%). BPD was diagnosed in 11 patients who survived beyond 36 weeks of gestation. The characteristics and outcome of 29 infants with viridans streptococcal positivity in BAL are described in Table 4. Susceptibility patterns of viridans streptococci are given in Table 5. Multi-drug resistance was observed in all viridans streptococci. There was no vancomycin resistance.

Laryngoscope blades and handles showed evidence of microbial contamination with the same multi-resistant streptococci.

TABLE 4. *Clinical characteristics of infants with viridans streptococci (% unless specified otherwise).*

Characteristic	Viridans streptococci-positive, $n=29$
Birthweight, g (SD)	1944 (956)
Gestational age, w (SD)	32.5 (4.2)
Males	20 (69)
Caesarean section	21 (72.4)
Age at onset of ventilation, d (SD)	2.5 (3.9)
Duration of ventilation, d (SD)	9.9 (10.3)
Duration of hospitalisation, d (SD)	37.5 (28.2)
Day of bacterial growth, d (SD)	5.1 (3.7)
Previous antibiotic administration	17 (58.6)
Died (%)	5 (17.2)
Mortality caused by infection	3 (10.3)
Colonisation	9 (31)
VAP	15 (51.7)
VAP infection rate (/1000 ventilation days)	52
Sepsis	5 (17.2)
BPD, $n=25$	11 (44)

TABLE 5. *Susceptibility patterns of viridans streptococci.*

Antibiotics	Susceptibility	MIC
Trimethoprim–sulphamethoxazole	R	>4
Ampicillin	R	8
Cefazolin	R	>16
Cefotaxime	R	>4
Gentamicin	R	>16
Clindamycin	R	0.5
Erythromycin	R	>8
Ciprofloxacin	R	=4
Vancomycin	S	0.5

MIC, minimum inhibitory concentration; R, resistant; S, sensitive.

Discussion

Nosocomial infection in neonates usually occurs after colonisation of the skin, pharynx or intestine by potentially pathogenic micro-organisms. The risk of infection increases dramatically if a neonate is in intensive care, ventilated and has a central venous or arterial catheter. Mechanical ventilation increases the occurrence of VAP.[1–5,14,18,20] However, diagnosing VAP in VLBW infants is difficult because the Centers for Disease Control and Prevention's definition is not specific to this population, an isolated positive tracheal culture alone does not distinguish between bacterial colonisation and respiratory infection,[21] and the clinical and laboratory signs of VAP are non-specific in neonates with BPD because the underlying disease complicates the interpretation of radiographic changes.[2,21] In our study, 29 patients with a positive BAL culture had viridans streptococci and 15 (52%) of these had VAP. In contrast with our study, gram-negative micro-organisms are often isolated as a major pathogen causing VAP in neonates.[2]

Viridans streptococci are important commensals of the respiratory and female genital tracts[9] that are rarely recovered from the skin and are not considered part of the normal skin flora. Despite the absence of viridans streptococci on the skin, blood cultures with these organisms are often considered to represent contamination. It is probable that they are usually low-grade pathogens that produce transient bacteraemia with small numbers of bacteria. Many cases may recover without antibiotics. Recent studies have demonstrated the potential of viridans

streptococci to produce bacteraemia in immunocompromised individuals, especially premature newborns.[8] Treatment becomes essential in the presence of an intravascular infection associated with endocarditis or when the host is immnocompromised.[8–10]

After the emergence of multi-resistant viridans streptococcal infection in our NICU, environmental samples were taken from incubators, humidifiers, suction jars, soap, intravenous solutions and laryngoscope blades and handles. The latter showed evidence of severe microbial contamination with the same multi-resistant viridans streptococci. In our unit the usual cleaning practice was to wash the neonatal blade in hot water and detergent, then wipe with an alcohol-impregnated wipe.

Laryngoscopy is an invasive procedure involving contact with mucous membranes, saliva and sometimes blood.[22] Mixed cultures have been grown from laryngoscopes following routine use, including a wide range of potentially harmful micro-organisms.[22–26] Possible cross-infection from laryngoscopes has been described in a delivery suite and in an NICU associated with *Listeria monocytogenes* and *Pseudomonas aeruginosa*.[25,26] Ballin *et al*. reported a high rate of microbial contamination on laryngoscope blades and handles deemed ready for patient use by an anaesthetic nurse. A significant number of blades and handles grew viridans streptococci (handles 93%, blades 73%).[27] Beamer *et al*. also reported MRSA contamination of laryngoscopes blades which appeared to be clean after being scrubbed with a plastic re-usable brush and chlorhexidine.[28] Potentially, pathogenic organisms could be transferred from one patient to another via equipment used routinely in NICUs. There should be nationally applicable quidelines for laryngoscope decontamination and a practical means of sterilising basic equipment.[29–31]

Mechanically ventilated neonates in our NICU had high rates of multi-resistant viridans streptococus airway colonisation, subsequent ventilator-associated pneumonia and sepsis. A major environmental reservoir of the micro-organism seemed to be laryngoscope blades and handles.

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