Prospective Surveillance of Nosocomial Infections in a Swiss NICU: Low Risk of Pneumonia on Nasal Continuous Positive Airway Pressure?

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Abstract

Background: This study assessed the rate of invasive nosocomial infections in very low birth weight (VLBW) ≤ 1,500 g infants in a Swiss university hospital neonatal intensive care unit (NICU). Device-association and device-related infection rates were prospectively evaluated.

Patients and Methods: From October 1999 to September 2000, 76 hospitalized neonates with VLBW were included, plus 60 neonates > 1,500 g, who had received a central venous or umbilical catheter, or assisted ventilation. Nosocomial infections (sepsis, pneumonia, necrotizing enterocolitis [NEC]) were defined according to Centers for Disease Control (CDC) recommendations with slight modifications and their rates measured longitudinally.

Results: Among VLBW neonates, 16 nosocomial infections for an overall infection rate of 6 per 1,000 patient days were found. Infants with infection were of lower birth weight, a greater proportion was male, received lipid infusions, and on average had a higher severity of illness (CRIB) score. Interestingly, the ventilator-associated pneumonia (VAP) rate (12.5/1,000 ventilator days) seemed significantly higher than the pneumonia rate during nasal continuous positive airway pressure (NCPAP) treatment (1.8/1,000 NCPAP days; p = 0.04). The sepsis rate associated with peripheral catheters almost equaled the central line-associated rate, although numbers for both device-related infections were small.

Conclusion: Further studies are needed to confirm the observation that the NCPAP-associated pneumonia rate might be lower than the VAP rate in VLBW infants, as well as to confirm the second observation that the sepsis rates on peripheral catheters compared to central venous catheters might be almost equal in VLBW infants. Reducing the exposure to ventilation via endotracheal tube, but not using peripheral as opposed to central catheters, might reduce the incidence of device-associated infection in this patient population.

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Introduction

Patients in neonatal intensive care units (NICU), especially neonates of very low birth weight (VLBW) ≤ 1,500 g, have the highest nosocomial infection (NI) rates among all pediatric patients. Reported infection rates in VLBW neonates vary between 13.4 and 83.6 infections per 100 patients and 7.3 to 20.7 infections per 1,000 patient days [1, 2]. Sepsis, pneumonia and necrotizing enterocolitis (NEC) are clinical entities carrying a high morbidity and mortality in this patient group. The use of indwelling devices such as intravascular catheters and endotracheal tubes contribute significantly to infection risk. VLBW infants with late onset sepsis are more likely to die than those uninfected, and strategies to reduce late infections are urgently needed [3].

The choice of a less invasive care strategy whenever possible should help to reduce the risk of nosocomial pneumonia in VBLW infants. Nasal continuous positive airway pressure (NCPAP), with plastic prongs in the nares or a plastic tubing ending in the pharyngeal space of the infant, as opposed to an endotracheal tube, can be considered less invasive; and infectious complications of the device "NCPAP" have been described rarely [4]. Even though NCPAP tubing does not reach the trachea, they are, however, connected to humidifiers and tubing comparable to ventilator circuits, and plastic tubing or prongs are in close

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contact with mucous membranes of the patient and nasal prongs may cause skin breakdown at the nares.

Surveillance has been identified as an important strategy for the control of nosocomial infections and the identification of risk factors [5]. In the American National Nosocomial Surveillance (NNIS) system the incidence of endotracheal tube-associated infections in neonates has been surveyed over time [3, 5, 6]. Outside the United States, there has been a paucity of data regarding infectious risks of intubation and ventilation in neonates. A difficulty of such studies lies in defining neonatal pneumonia, especially while primary respiratory distress syndrome (RDS) of prematurity or, later in the hospital course, chronic lung disease (CLD) coexist in VLBW infants [7, 8], both carrying radiological signs easily mimicking lung infection [9].

Ventilation as well as infection have long been linked to an increased incidence of CLD [10], a major sequel of premature birth, although infection acquired at or before birth may be larger contributory factors [11].

Central venous catheters (CVCs) are generally considered to bear a higher infection risk than peripheral venous catheters (PVCs). In VLBW infants, this has not been studied intensively.

This study assessed device-associated nosocomial infection rates in a cohort of 76 VLBW neonates and 60 neonates with a birth weight > 1,500 g with a central venous or umbilical catheter or assisted ventilation.

Patients and Methods

This surveillance study was conducted between October 1999 and September 2000 in the NICU located at the University Hospital for Obstetrics and Gynecology, Bern, Switzerland. The department has five beds for intensive care, 11 beds for intermediate care and five beds for continuous care of neonates. Ventilation, NCPAP and umbilical lines were in use exclusively in the five intensive care beds.

All VLBW neonates hospitalized during the study period were included in the surveillance. In addition, neonates with a birth weight of > 1,500 g who received a central venous or umbilical catheter or assisted ventilation via endotracheal tube and a ventilator (ETV), or via NCPAP were surveyed. Both these techniques of assisted ventilation were described in detail by *Gitterman* et al. [12]. Study patients had to be hospitalized at least 48 h to be included. Two investigators not involved in patient care (B.B. and K.S.) followed study neonates prospectively until discharge (or death). Information on socio-demographic and clinical characteristics was abstracted from the patients' charts using a standardized form. The clinical risk index for babies (CRIB) score was recorded as a measure of morbidity in each patient [13].

The following nosocomial infections were surveyed: sepsis, pneumonia, catheter-related infection, and NEC. The CDC definitions for nosocomial infections were applied with modifications for sepsis and pneumonia to suit age-specific findings in neonates and premature infants ≤ 28 d after their estimated due date according to *Gastmeier* et al. [14]. Infections occurring < 48 h after birth or < 48 h after admission to the unit were not classified as nosocomial. An infection was called device-associated if a device was present during the 48 h preceding the diagnosis of infection and no other focus was identifiable. Device-utilization rates were calculated according to *Gaynes* et al. [5]. The use of NCPAP was stratified into continuous and intermittent usage.

The χ^2 test or Fisher's exact test was used to compare categorical data and rates. Comparison of nonparametric data was done using the Mann-Whitney test. All calculations were done using the software StatView® version 5.0 (SAS Institute Inc., Cary, NC). Differences were regarded statistically significant, if the p-value was < 0.05 (α two-tailed).

Results

Between October 1999 and September 2000 a total of 136 study patients were recruited, 76 VLBW infants and 60 neonates with a device. Device-utilization rates were comparable between VLBW infants and neonates > 1,500 g with the exception of NCPAP use, which was higher for VBLW infants ($p < 0.001$) (Table 1). None of the study patients received a CVC during the surveillance period.

Clinical characteristics of the study patients are given in table 2. As expected, VLBW neonates, on average, had a higher CRIB score and stayed longer in the unit than neonates > 1,500 g.

Among the VBLW neonates, 16 nosocomial infections were recorded (21.1% infections and 18.4% infected patients) for an infection rate of 6 per 1,000 patient days. Infants with infection were of lower birth weight, a greater proportion was male, received lipid infusions, and on average had a higher CRIB score. The nosocomial infections and device-specific infection rates are given in table 3. None of the sepsis events was associated with an umbilical catheter. The sepsis rate associated with a peripheral line was 10.0 per 1,000 line days. Intravascular catheter infections were seen only in association with an umbilical catheter and none with a peripheral catheter.

The rate of ventilator-associated pneumonia (VAP) (12.5/1,000 ventilator days) was significantly higher than the pneumonia rate during continuous NCPAP treatment (1.8/1,000 NCPAP days; $p = 0.04$). No pneumonia was seen during intermittent NCPAP treatment. VLBW neonates with infection had a significantly lower birth weight ($p = 0.01$), were more often male ($p = 0.03$), received lipid therapy more frequently ($p = 0.01$), more often had more than one course of antibiotic treatment ($p < 0.001$) and received more often endotracheal intubation ($p = 0.05$) than neonates without an infection (Table 2).

Only one infection (1.7 %), a clinical sepsis, was seen among neonates > 1,500 g for an infection rate of 0.9 per 1,000 patient days. This infection was not associated with any device.

Mortality among the study patients was 2.9% (4/136). Two neonates died from malformations. A nosocomial infection was not implicated in any of the deaths. The other two patients died on their 3rd day of life secondary to problems related to extreme prematurity (CRIB score 16 and 7, birth weight 520 g and 480 g).

Table 1
Device utilization among 76 very low birth weight neonates and 60 neonates with birth weight > 1,500 g.

	≤ 1,500 g		> 1,500 g	
	No.	%	No.	%
Patients	76		60	
Patient days	2,681		1,048	
Umbilical catheter	23	30.2	11	18.3
Catheter days/mean	129/5.6		43/3.9	
Catheter utilization rate		4.8		4.1
Peripheral catheter	73	96.1	60	100
Catheter days/mean	804/11.0		466/7.8	
Catheter utilization rate		30.0		44.5
Endotracheal intubation (ETV)	21	27.6	10	16.7
Tube days/mean	80/3.8		27/2.7	
Tube utilization rate		3.0		2.6
Nasal continuous positive airway pressure (NCPAP)	61	80.3	56	93.3
Continuous/intermittent days	563/610		104/72	
Total NCPAP days/mean	1,173/19.2		176/3.1	
Total NCPAP utilization rate		43.8		16.8

Discussion

Overall, previously well-known risk factors for infection were present in a higher proportion of infected infants than in non-infected infants, that is male gender, lipid infusion, higher CRIB score, and endotracheal intubation.

Special emphasis was put on device-associated infection in VLBW neonates, and neonates > 1,500 g birth weight with a device. Specifically, pneumonia rates associated with endotracheal intubation and ventilation (VAP) were compared to pneumonia rates associated with NCPAP.

As a means of treating respiratory disease states which affect most VLBW infants, several indications for NCPAP exist: apnea of prematurity, following extubation, and early NCPAP for RDS of prematurity [15–17]. The concept of "permissive hypercapnia" may have influenced many neonatology centers to adopt NCPAP as an alternative to mechanical ventilation in a controlled manner [3] or via slow attitude or practice change favoring less intubation [18]. Theoretically, NCPAP is associated with fewer side effects than mechanical ventilation, but the reduced association with nosocomial infection has not been measured. In a premature baboon model of NCPAP use and long-term bronchopulmonary dysplasia (used synonymously with the term CLD in humans in this context), where the lungs were studied histologically at 28 days, no evidence of pneumonia was seen in the five NCPAP-exposed animals [19].

Even though the absolute numbers of one pneumonia in each group – one on NCPAP and one under ventilation – are small, the finding in this study of 1.8 pneumonia episodes per 1,000 continuous NCPAP days as opposed to 12.5 such episodes per 1,000 mechanical ventilation days generates the hypothesis that one of the important gains of NCPAP for immature patients may be attributed to a reduced risk of nosocomial pneumonia. Meanwhile, NCPAP-associated nosocomial infection rates have been monitored continuously since 2000 by the German Neo-Kiss system [20] operating in a similar manner as the NNIS system, with cumulative rates compiled from several centers for comparison. The 2-year Neo-Kiss report of 2000/2, based on 3,357 VLBW infants, has a pooled CPAP-associated infection rate of 1.3 versus an ETV-associated infection rate of 2.9 (personal communication, *C. Geffers*, NeoKiss, current data available at [20] in a report stratified by even smaller birth weight steps). Since the Neo-Kiss definitions of nosocomial infection [20] are the same as the ones used in this single-center study, the results may be compared and more valid conclusions be drawn from the multi-center NeoKiss data. The pneumonia rate observed in the current study can be placed below the 50th percentile (for intermittent NCPAP) and at the 75th percentile (for continuous NCPAP) of the Neo-Kiss report during the same time period. Hence, the infection risk associated with ETV might be twice the risk associated with NCPAP.

Table 4 gives an overview of previously published, device-associated VAP rates. All studies dealing with the diagnosis or surveillance of VAP (analogous: NCPAP-AP) are hampered by the still unresolved issue of (in)accuracy of radiologic criteria and difference of even expert opinion about presence or absence of radiological signs of pneumonia in VLBW infants. This dilemma has been described in detail by *Cordero* et al [8]. This, however, was one of the

Table 2
Clinical characteristics of 76 very low birth weight neonates ≤ 1,500 g, and 60 neonates > 1,500 g, with or without nosocomial infection.

	≤ 1,500 g				> 1,500 g	
	No infection*		Infection*			
	No.	%	No.	%	No.	%
Patients	62		14		60	
Birth weight (g) median	1,105		830		2,030	
Range	420–1495		620–1,390		1,520–4,775	
Gestational age (wks) mean	29.0		28.0		33.4	
Range	25.2–34.3		25–33.3		29.2–41.1	
Female gender	37	59.7	4	28.6	20	33.3
CRIB [13] score						
0–5	49	79	8	57.1	58	96.7
6–10	12	19.4	6	42.9	2	3.3
11–20	3	4.8	0	0	0	0
Length of stay						
Mean	33.2		44.6		17.4	
Range	2–104		6–102		2–52	
Lipid therapy	27	43.5	11	78.6	3	5.0
Antibiotic therapy						
< 48 h of age	29	46.8	8	57.1	23	38.3
> 48 h of age	9	14.5	14	100	3	5
Therapy courses per patient						
0	26	41.9	0	0	35	58.3
1	33	53.2	6	42.9	24	40.0
> 1	3	4.8	8	57.1	1	1.7
Umbilical catheter	17	27.4	6	42.9	11	18.3
Catheter days/mean	95/5.6		34/5.7		43/3.9	
Catheter utilization rate		4.6		5.4		4.1
Peripheral catheter	59	95.2	14	100	60	100
Catheter days/mean	557/9.4		247/17.6		466/7.8	
Catheter utilization rate		27.1		39.6		44.5
Endotracheal intubation	14	22.6	7	50	10	16.7
Tube days/mean	47		33		27/2.7	
Tube utilization rate		2.3		5.3		2.6
NCPAP	48	77.4	13	92.9	56	93.3
Continuous/intermittent days	364/524		199/86		56/104	
Total NCPAP days/mean	888/18.5		285/22.0		176/3.1	
Total NCPAP utilization rate		43.2		45.7		16.8

NCPAP: nasal continuous positive airway pressure; wks: weeks; * Statistical comparison of neonates with and without infection resulted in significant p-values for birth weight (p = 0.01), gender (p = 0.03), lipid therapy (p = 0.01), >1 courses of antibiotic therapy as compared to 0 or 1 courses (p <0.001), and endotracheal intubation (p = 0.05)

main reasons for the non-literal use of CDC criteria for infants < 1 year of age and specification of those criteria in our study according to *Gastmeier* et al. [14], also used in the same manner in the German Neo-Kiss system [20]. At least for the latter system, the extremely large number of patients and ventilator days prospectively surveyed with identical criteria ascertains a real difference between NCPAP- and ventilator-associated pneumonia rates for VLBW infants.

Long duration of mechanical ventilation is also significantly associated with late onset sepsis in VLBW infants; data "suggest that decreasing the number of days on the ventilator…might reduce the rate of infection" [3]. Sepsis and pneumonia are not easily distinguishable clinically in premature infants, thus making it likely that an overlap exists between sepsis and pneumonia data stemming from premature infants. In adult intensive care, where pneumonia can be much better defined and distinguished from sepsis alone or in combination, such observations have been made as well. Among other morbidities associated with intubation and ventilation, VAP-associated infections led to guidelines and recommendations to avoid intubation whenever possible and favor noninvasive ventilation [21].

The ETV-associated pneumonia rate in this study appears high as compared to published data (Table 4). Another single-center study, carried out 1 year later, showed a VAP rate of 6.5 per 1,000 ventilator days in infants < 28 weeks gestational age, using original CDC criteria for infants < 1 year of age [22] but methodologically debated: it is accompanied by an editorial demanding new definitions for VAP in premature neonates [9] – a process which in the origins of the NeoKiss system ultimately has led to the modified definitions used for premature infants published by *Gastmeier* et al. [14, 20] and used in this study. Another reason for a seemingly high rate of VAP may be the consequence of more frequent use of NCPAP in the first place (effect of usage and training), single-center or small-number effects, and restriction of ETV to critically ill infants. Published infection rates, such as the NNISS and Neo-KISS data, are stratified according to birth weight only, not according to morbidity. With increasing use of NCPAP in VLBW neonates, adjustment for severity of illness may become necessary for a valid comparison of pneumonia rates between centers. In Europe, the CRIB score is the most widely used severity of illness score for neonates [13]. CRIB-stratified infection rates, however, cannot be deducted from this study due to the small number of patients actually infected, a possible limitation of our data.

The sepsis rate associated with PVC observed in this study was 10.0 per 1,000 line days. This is in accordance with the rate reported in the Neo-Kiss system. Surprisingly, this rate is close to the rate observed for CVC sepsis. In other words, peripheral access could entail as high a risk of infection as central venous access in VLBW infants – probably caused by an immature skin defense or other factors in the immature immune system indicating that "catheter-associated" infections are not necessarily caused by the line itself. It also underlines the much higher infection risk of PVCs in VLBW neonates compared to the risk observed in older children and adults, or, *vice versa*, a lack of advantage of PVCs as compared to CVCs. One Canadian study found an even smaller rate of infection in percutaneously inserted central venous catheters (PCVCs) as compared to multiple insertions of peripheral lines for a cohort of

Table 3
Nosocomial infection rates among 76 neonates with birth weight ≤ 1,500 g.

	No.	%
Infected patients	14	18.4
Nosocomial infections	16	21.1
Infection rate/1,000 patient days	6.0	
Sepsis	11	14.5
Clinical sepsis/ laboratory confirmed sepsis	9/2	11.8/2.6
Sepsis/1,000 patient days	4.1	
Peripheral line-associated	8	72.7
Sepsis/1,000 peripheral line days	10.0	
Pneumonia	2	2.6
Ventilator-associated (VAP)	1	50.0
Rate/1,000 ventilator days	12.5	
NCPAP-associated (NCPAP-AP)	1	50
Rate/1,000 total NCPAP days	0.9	
Rate/1,000 continuous NCPAP days	1.8	
Intravascular catheter infection	1	1.3
Rate/1,000 patient days	0.4	
Umbilical line-associated	1	100
Rate/1,000 umbilical catheter days	7.8	
Necrotizing enterocolitis	2	2.6
Rate/1,000 patient days	0.7	

Table 4
Device-associated nosocomial infections (incidence-density/1,000 device-days) in very low birth weight infants obtained in previous studies using CDC criteria and methodology.

	CVC/sepsis	Device/infection UMC/sepsis	PVC/sepsis	VAP	NCPAP-AP
This study[a]	N.A.	0	10.0	12.5	1.8
Ferguson 1996 [24]				7.3	
Ng 1998 [25]				1.0	
Gastmeier 1998[a] [14]		10.7		4.3	
Neo-Kiss 2000/1[a] [20]		13.9	10.0	2.9	1.5
NNISS 2001 [26]					
≤ 1,000 g		11.3		4.8	
1,001–1,500 g		6.9		3.6	

[a] CDC criteria modified for neonates; N.A.: not applicable; CVC: central venous catheter; UMC: umbilical catheter; PVC: peripheral venous catheter; VAP: ventilator-associated pneumonia; NCPAP-AP: nasal continuous positive airway pressure-associated pneumonia

infants of extremely low birth weight, < 1000 g [23]. In conclusion, central catheters may not expose VLBW neonates to a higher rate of infection, compared to peripheral venous access. This is another area needing further study for this patient population, as we did not investigate venous access duration or frequency of catheter change, nor rates of thrombophlebitis.

As a second conclusion, in our unit with high usage of NCPAP in our NICU the device-associated pneumonia rate appeared to be lower than the risk associated with ETV. More widespread and earlier use of NCPAP to limit endotracheal tube and ventilation use, but not preference of peripheral over central venous access, may be measures to reduce morbidity and mortality in premature infants. Larger studies with the inclusion of risk stratification are necessary to confirm our observations.

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