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Infections and risk-adjusted length of stay and hospital mortality in Polish Neonatology Intensive Care Units

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ABSTRACT

Background: The objectives of this study were to analyze the impact of infections on prolonging hospital stay with consideration of underlying risk factors and determining the mortality rates and its association with infections.
Methods: An electronic database developed from a continuous prospective targeted infection surveillance program was used in the study. Data were collected from 2009 to 2012 in five Polish tertiary academic neonatal intensive care units (NICUs). The length of stay (LOS) of 2,003 very low birth weight (VLBW) neonates was calculated as the sum of the number of days since birth until death or until reaching a weight of 1,800 g.
Results: The median LOS for neonates with infections was twice as high as for neonates without infection. LOS was significantly affected by the overall general condition of the neonate, as expressed by both gestational age and birth weight as well as by the Clinical Risk Index for Babies (CRIB) score; another independent factor was presence of at least one infection. Risk of in-hospital mortality was significantly increased by male sex and vaginal birth and was lower among breastfed neonates. Deaths were significantly more frequent in neonates without infection.
Conclusions: The general condition of VLBW infants statistically increase both their risk of mortality and LOS; this is in contrast to the presence of infection, which significantly prolonged LOS only.

1. Introduction

Nosocomial infections are one of the most frequent adverse events among hospitalized patients and are a threat to all patients. However, in some patient populations (e.g., those undergoing surgical procedures and in intensive care units [ICUs]), the risk of acquiring a nosocomial infection is particularly high. Among infants hospitalized in ICUs, and especially those of very low birth weight (VLBW), there is a greater risk of acquiring an infection. The increased risk of infection in this neonatal population is associated with a lower gestational age (as extremely premature infants have thinner, more permeable skin, underdeveloped innate and adaptive immune responses, and immature mucous membranes) and their underlying illness,[1,2] as well as the requirements for invasive therapies, such as central venous intravenous catheters, and the hygiene practices of health care providers.

The most frequent infections in neonatal intensive care units (NICUs) are bloodstream infections, pneumonia, and necrotising enterocolitis (NEC); less frequent complications are infections of the urinary tract and the central nervous system.[3,4] Infections among VLBW infants may, directly or indirectly, result in the death of an infant; however, even with effective treatment, infections in this population may be associated with a prolonged length of stay (LOS).

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Payne et al., in their study of 17 hospitals in the United States, determined a 19.7% incidence of central line-associated bloodstream infections (CLABSIs), which were associated with an increase in the marginal cost of hospitalization for a single neonate from $5,875 to $12,480. Rates of ventilator-associated pneumonia (VAP) in the NICU were reported in the range of 0.2 to 1.6 per 1000 person-days of ventilation, according to 2011 data reported in National Healthcare Safety Network (NHSN) in the United States.[3] According to the NHSN, VAP in NICUs accounted for approximately one-fifth of all infections, and CLABSIs for nearly 80%. In a study by Rosenthal et al., crude rates for excess mortality associated with CLABSIs and VAP were determined to be 27.7% and 17.9%, respectively.[5]

The objectives of the present study were to determine:

1) the association between the presence of infections in VLBW neonates and the LOS for neonates surviving until they reach a weight of 1,800 grams;
2) the association between the presence of infections and in-hospital mortality; and
3) if infection is an independent risk factor for the above mentioned outcomes, with consideration of other risk factors unrelated to infection,

2. Materials and methods

An electronic database, created as a result of continuous prospective surveillance of infections, that focused on VLBW neonates was used in the study. Data were collected between January 1, 2009 and December 31, 2013 at five tertiary academic NICUs that took part in the Polish Neonatology Surveillance Network (PNSN). The PNSN is a prospective national surveillance system for the most relevant infections in VLBW infants (birth weight <1,500 g) in Poland. These urban tertiary teaching hospital NICUs provide care for 20% of all VLBW infants born in Poland annually. Details of the following variables were collected for all VLBW infants: birth weight and gestational age, gender, multiple pregnancy, type of delivery, information on the situation at the time of delivery (e.g., chorioamnionitis), general physical state as measured by Apgar scores at 1 and 5 minutes and the Critical Risk Index for Babies (CRIB) score, and detailed data on antibiotic treatment. The PNSN recorded severe infections, including bloodstream infections (CLA-BSI and other cases of BSI) and pneumonia (PNEU), observed during hospitalization (from admission to discharge, transfer, or death). NICU participation in the PNSN was voluntary and confidential.

Utilisation of data collected by the PNSN for scientific purposes was approved by the Bioethics Committee of Jagiellonian University Medical College (no. KBET/221/B/2011). All data entered into the electronic database and analysed during the compilation of this article were previously de-identified. Data were obtained during routine treatment and diagnostic procedures performed during patients' hospitalisation. Before analysis, incomplete records (without date of birth/discharged/death; gender; data about infections) were deleted and, as a result, complete records of 1,038 neonates without infections and 965 neonates with BSIs, PNEU, or other types of infection were available.

Neonates with birth weight less than 1,500 g (considered as VLBW) were included in the study. Cases of early and/or late infections (BSI, PNEU, NEC) in neonates (only with clinical signs of infection) were defined according to Gastmeier et al.[6], with some modification. Standard indicators of the general state of neonates were Apgar scores (at 1 and 5 minutes) and CRIB scores. Diagnosis of chorioamnionitis was based on clinical evaluation without the need for microbiological or histopathological examination.[7] Determination of the microbial species and evaluation of drug resistance were conducted by local microbiologic laboratories.

The device utilization rate (calculated by dividing the number of device days by the total number of patient days) was 0.45 for central venous catheters (CVCs), 0.16 for peripheral intravenous catheters (PVCs), 0.25 for mechanical ventilation (MV), and 0.18 for continuous positive airway pressure (CPAP). LOS for neonates in the NICU was calculated as the sum of the number of days since birth until death or discharge from the hospital. In three of the five participating NICUs, this occurred at reaching 34 to 35 weeks of gestational age and in two, on reaching a weight of 1,800 g.

Data were analysed in two ways. The relationship between particular clinical effects and single elements of care procedures were investigated with univariate statistics. The selection of statistical techniques depended on the type and distribution of the variables analysed. If both dependent and independent variables were categorical, qualitative frequency tests such as chi square or likelihood ratio were used. If the dependent variable was continuous (e.g., LOS or birth weight) and the predictors were qualitative, the Mann-Whitney U test for dichotomous predictors or Kruskal-Wallis test were calculated. More powerful parametric tests (e.g., analysis of variance or student t-test) could not be used because of non-normal distribution of the dependent variables. Common effects of several variables on mortality probability were analysed with a generalized linear model. Because of the dichotomous character of the effect and different types of predictors, a model was constructed with an assumption of a binominal distribution of the dependent variable and logit-linked function. The assumed critical value of the significance level was $p < 0.05$.

3. Results

The PSNS included 2,003 VLBW neonates, including 372 extremely low birth weight infants (18.6%) with a birth weight up to 750 g, 516 infants (25.8%) with birth weight ranging from 751 to 999 g, and 1,115 infants (55.7%) with birth weight ranging from 1,000 to 1,500 g (Table 1).

3.1. Risk of infection

The risk of infection significantly correlated with birth weight; the strongest correlation was found in neonates with birth weights ranging from 750 to 999 g (Table 1). Also, delivery at 28 weeks gestation or earlier was associated with a 3.5-fold higher risk of infection as compared to VLBW neonates born at 28 weeks gestation or later. Significance of the correlation between infection and interventions such as CVC, MV, and CPAP, and medians days of use of these interventions was determined; risk of infection in neonates with exposure to these interventions was five to ten times higher compared to no exposure (Table 1). Neonates with infections were treated with antimicrobial agents for a mean of 19 days.

3.2. In-hospital mortality

Median birth weight and gestational age of neonates who died were significantly lower, similar to general neonate condition expressed by Apgar scores at 1 and 5 minutes. The highest mortality rate was found in neonates with birth weight less than 750 g (50.5%) and/or delivered in the 28th week of gestation or later (30.1%). However, risk of in-hospital mortality was significantly increased by male sex and vaginal birth. The risk of

Table 1
Baseline characteristics of VLBW newborns with and without infections

Baseline characteristics	Infants with infections N = 965	Infants without infections N = 1038	OR (95%CI)	p
median birth weight (grams) (IQR)	960 (770 – 1200)	1150 (890 – 1340)	NA	<0.001
<750 grams n (%)	208 (21.6)	164 (15.8)	1.46 (1.167-1.837)	<0.001
750-999 grams n (%)	326 (33.8)	190 (18.3)	2.28 (1.853-2.799)	<0.001
1000-1249 grams n (%)	241(25.0)	281 (27.1)	0.897 (0.734-1.095)	<0.001
1250-1499 grams n (/%)	190 (18.5)	403 (38.0)	0.39 (0.316-0.473)	<0.001
median gestational age / (IQR)	28.0 (26 – 30)	29.0 (27 – 31)	NA	<0.001
less than or equal to 28 weeks n (%)	626 (64.87)	355 (34.20)	3.55 (2.955- 4.271)	<0.001
more than 28 weeks n (%)	339 (35.13)	683 (65.80)		<0.001
female sex n (%)	442 (46.53)	508 (53.47)	0.88 (0.7397 – 1.051)	-
male sex n (%)	523 (49.67)	530 (50.33)		-
CC n (%)	766 (47.25)	855 (52.75)	0.82 (0.658 – 1.030)	-
vaginal birth n (%)	198 (52.11)	182 (47.89)		-
breastfeeding n (%)	79 (42.02)	106 (56.38)	0.78 (0.578 – 1.064)	0.019
CVC [days] median (IQR)	11 (0 – 24)	1 (0 – 8)	NA	<0.001
MV [days] median (IQR)	5 (0 – 19)	1 (0 – 20	NA	<0.001
CPAP [days] median (IQR)	8 (2 – 18)	0 (0 – 3)	NA	<0.001
antibiotics [days] median (IQR)	19 (13-29)	4 (1 – 7)	NA	<0.001
CRIB median (IQR)	4 (1 – 7)	2 (1 – 7)	NA	-
Apgar 1 median (IQR)	6 (4 – 7)	6 (4 – 7)	NA	<0.001
Apgar 5 median (IQR)	6 (5 – 7)	7 (5 – 8)	NA	<0.001
chorioamnionitis n (%)	76 (53.15)	67 (46.85)	1.24 (0.881-1.742)	-
PROM n (%)	268 (56.07)	210 (43.93)	1.52 (1.233-1.864)	<0.001
multiple birth n (%)	221 (42.26)	302 (57.74)	0.72 (0.592-0.885)	0.002
Outcomes				
LOS [days] median /(IQR)	44 (29 – 58)	22 (1 – 13)	NA	<0.001
Discharge n (%)	779 (56.65)	596 (43.35)	3.106 (2.538-3.801)	<0.001
Transfer n (%)	101 (33.33)	202 (66.67)	0.49 (0.374-0.626)	<0.001
Died n (%)	85 (26.23)	239 (73.77)	0.32(0.247-0.421)	<0.001

IQR - Interquartile Range; OR odds ratio; 95% CI 95% confidence interval; NA not available.
CC Caesarean section; CPAP continuous positive airway pressure; CRIB Critical Risk Index for Babies; CVC central venous catheter; LOS length of stay; MV mechanical ventilation; PROM premature rupture of membranes; VLBW very low birth weight.

in-hospital mortality was lower in breastfed neonates, showing strong trend (p = 0.019; OR 0.78; 95% CI 0.578-1.064) – Table 1.

Invasive procedures (CVC, PVC, MV, CPAP) were used for a longer period of time in the neonates who survived to hospital discharge in comparison with neonates who did not survive (Table 2). Neonatal deaths were significantly more frequent among neonates without infection (Table 1), and, at the same time, the average LOS was 19 times shorter (because of early deaths) compared to surviving neonates who were discharged from the NICU (Table 2).

3.3. Length of hospital stay

The median LOS for all neonates with infections was twice as high as for neonates without infection (44 days vs. 22 days) – Table 1. However, taking into consideration only neonates who were discharged from the NICU as a result of achieving their expected birth weight (i.e., a successful treatment), the median stay for neonates without infection was longer - 30 days, compared with a median stay of 45 days for neonates with at least one type of infection – Table 2. Moreover, specific infections or multiple infections in a neonate affected LOS to varying degrees. The occurrence of more than two types of infection resulted in a two-fold prolongation of LOS for neonates in the NICU (60 days vs. 30 days without infections); PNEU and BSI were associated with a longer LOS, by approximately 20 days (Table 2).

3.4. Independent predictor of length of stay by multivariate analysis

The LOS in the NICU was significantly affected by the general overall condition of the neonate, expressed by both gestational weight and gestational age as well as CRIB scores. The other independent factor was the presence of at least one infection.

4. Discussion

Infections in neonates, particularly those with the lowest weight, remain one of the most important problems in modern medicine. One issue is an increasing number of premature births, as well as the increase in multiple pregnancies.[8,9] Another cause might be the improvement in the survival rate of VLBW neonates in modern NICUs, which are better equipped for life-saving intensive care nowadays than in the past.

Our results for mortality and LOS are the first to be reported by the PNSN and from Central Europe based on a national program for infection surveillance and control in NICUs. Our previous report on this population within the PNSN focused on various types of infection or their aetiology.[10–13] In the study population, the epidemiology and microbiology of infections did not differ from data obtained in other multi-setting studies.[14,15]

It is thought that NICU admission and treatment may be connected with a high incidence and mortality rates related to both early- and late-onset infections.[16–22] In Poland, in a studied group of neonates with symptoms of early-onset infections (EOIs), an increased case-fatality rate was not observed. Early mortality (i.e., <7 days after delivery) was 17% for early-onset BSI and 8% for early-onset PNEU. The case-fatality rate associated with late-onset BSI was 7.5%.[10,11] However, our present results indicate that infections are not a significant factor for increasing VLBW neonatal mortality. The birth weight and gestational age proved to be more important. Also, other authors have confirmed our observations. Infants born at the threshold of viability (those with a gestational age of 23 to 25 weeks, a birth weight <500 g, or both) are at the greatest risk for a poor outcome. For example, in the Vermont Oxford Network (a voluntary network for data collection from more than 650 NICUs in the United States and worldwide), among infants born between 1996 and 2000 with a birth weight of 401 to

Table 2
In-hospital mortality of VLBW neonates in the PNSN

Baseline characteristics	Death in-hospital N = 324	Discharge N = 1375	OR (95%CI)	p
median birth weight (grams) (IQR)	750 (600 – 1000)	1105 (900 – 1320)	NA	<0.001
<750 grams n (%)	157 (50.48)	154 (49.52)	7.45 (5.662 – 9.812)	<0.001
750-999 grams n (%)	85 (20.00)	340 (80.00)	1.08 (0.821 – 1.427)	<0.001
1000-1249 grams n (%)	48 (11.06)	386 (88.94)	0.45 (0.321 – 0.619)	<0.001
1250-1499 grams n (/%)	34 (6.65)	495 (96.87)	0.21 (0.144 – 0.302)	<0.001
median gestational age / (IQR)	26.0 (24 – 28)	29.0 (27 – 31)	NA	<0.001
less than or equal to 28 weeks n (%)	261 (30.10)	606 (69.90)	5.26 (3.914 – 7.061)	<0.001
more than 28 weeks n (%)	63 (7.62)	764 (92.38)	0.19 (0.144 – 0.259)	<0.001
female sex n (%)	132 (16.42)	672 (83.58)	0.72 (0.563 – 0.919)	<0.001
male sex n (%)	192 (21.45)	703 (78.55)		
CC n (%)	224 (16.37)	1144 (83.63)	0.45 (0.342 – 0.593)	<0.001
vaginal birth n (%)	100 (30.30)	230 (69.70)		
breast feeding n (%)	3 (1.73)	170 (98.27)	0.07 (0.021-0.209)	<0.001
CVC [days] median (IQR)	1 (0 – 4)	7 (0 - 180	NA	<0.001
MV [days] median (IQR)	2 (1 - 60	1 (0 – 8)	NA	<0.001
CPAP [days] median (IQR)	0 (0 – 0)	5 (1 – 14)	NA	<0.001
antibiotics [days] median (IQR)	2 (1 – 6)	13 (6 – 23)	NA	<0.001
CRIB median (IQR)	8 (6 - 120	2 (1 – 5)	NA	<0.001
Apgar 1 median (IQR)	3 (1 – 5)	6 (5 – 7)	NA	<0.001
Apgar 5 median (IQR)	4 (1 – 6)	7 (6 – 8)	NA	<0.001
chorioamnionitis n (%)	25 (20.490	97 (79.51)	1.10 (0.697-1.740)	-
PROM n (%)	75 (18.07)	340 (81.93)	0.92 (0.689-1.220)	-
multiple birth n (%)	87 (19.33)	363 (80.67)	1.02 (0.779-1.345)	-
Outcomes: LOS (days)				
median /(IQR)	2 (0 – 8)	38 (27 - 530	NA	<0.001
No infection- median /(IQR)	0 (0 – 3)	30 (23 – 38)	3.68 (2.807-4.812)	<0.001
At least 1 infection- median /(IQR)	12 (4 – 23)	45 (32 – 59)	0.27 (0.208-0.356)	<0.001
BSI - median /(IQR)	12 (4 – 21)	48 (33 – 61)	0.38 (0.282-0.516)	<0.001
PNEU - median /(IQR)	19 (9 – 26)	51 (39 – 65)	0.29 (0.203-0.425)	<0.001
> one infection - median /(IQR)	26 (16 – 40)	60 (48 – 69)	0.32 (0.210-0.495)	<0.001

IQR - Interquartile Range; OR odds ratio; 95% CI 95% confidence interval; NA not available.
BSI bloodstream infection; CC Caesarean section; CPAP continuous positive airway pressure; CRIB Critical Risk Index for Babies; CVC central venous catheter; LOS length of stay; MV mechanical ventilation; PNEU pneumonia; PROM premature rupture of membranes; VLBW very low birth weight.

500 g and a mean gestational age of 23.2 weeks, the mortality rate was 83%.[23] This is similar to the rate among surveyed Polish VLBW neonates (75%).[10] The risk of death decreases significantly with an increase in birth weight.[24] Overall, in the group of VLBW neonates, general in-hospital mortality (not associated with infections) was 16.7% in Italy[25] and 14.3% in Korea.[26] In developing countries, in-hospital mortality is higher; 28.1% in Iran[27] and 35% in India.[28] Unfortunately, the neonates in-hospital mortality may also depend on other risk factors. In a study by Apisarnthanarak et al. regarding VAP in extremely preterm neonates, the in-hospital mortality rate was 27%. In such defined populations, VAP was the only significant risk factor for mortality.[29]

In nearly half (48.2%) of all studied VLBW neonates, at least one clinical infection developed during the time period studied. But it was found that infection was not a factor affecting the risk of neonatal death. Conversely, infections were observed mainly among the neonates that survived. Infection was one of the independent factors influencing the prolongation of the neonate's stay in the NICU. However, at the same time, the occurrence of one or more clinical infections, as well as the site of infection, had a variable effect on LOS. The occurrence of more than one infection was associated with the longest LOS for neonates in the NICU; the median LOS was 60 days versus 30 days for neonates without an infection. Among neonates who developed one infection, PNEU was associated with the highest median LOS as compared to neonates without an infection (51 days vs. 30 days). This value is only slightly higher than that for BSIs, where the median LOS was 48 days.

For studies regarding prolonged LOS by neonates in NICUs conducted by other authors, results that differ from the data presented in our work, were reviewed. Apisarnthanarak et al.[29] observed a median LOS for neonates with VAP almost three times higher than that for neonates in Polish NICUs (138 days [SD 13-361] vs. 82 days [SD 8-197]), where VLBW neonates accounted for only about 30%, with a median gestational age of 25 weeks. In the cited study, the median LOS for all neonates was 30 days (similar to the median LOS of VLBW neonates without infection in Polish NICUs) and 76 days for VLBW neonates. The differences in LOS seen in both studies may be due to different neonate populations included in the trials. In the US study, only neonates who required MV were eligible for inclusion, whereas in the Polish study, MV was used in a small percentage of neonates (utilization ratio: 0.25).

In a study by Payne et al.[30] conducted in 17 US hospitals that evaluated costs and prolonged LOS for VLBW infants with BSI, the mean LOS of neonates with BSI ranged from 48 to 101 days (depending on birth weight), compared with a mean LOS of 32 to 85 days for neonates without infections. The mean prolongation of LOS secondary to BSI was, therefore, recorded at the level from 13 to 17 days – the upper limit of this range is thus approximate to the result from Polish NICUs, i.e., the median prolongation of LOS by 18 days in neonates with BSI. The analysis of data by multivariate logistic regression demonstrated, however, an increase in LOS for VLBW neonates with BSI by 4 to 7 days and associated costs falling within the range from 5,875 USD to 12,480 USD. In contrast, Polish LOS values were similar to the results obtained in a German study (NeoKISS) by Denkel et al.[31]

Despite nearly 20 years of experience with modern infection control in Poland and the organisation of surveillance according to international standards,[32] there are virtually no studies concerning the cost of infections. And reports of this type, for both adults and neonates, are limited because of the socio-economic conditions and healthcare organizations in Poland.

An attempt to estimate the costs of NICU care for premature infants was undertaken by Krawczyk-Wyrwicka, who analysed costs in one NICU,[33,34] particularly the costs associated with BSI.

Table 3
Independent predictor of LOS of VLBW newborns, who were discharged from the ward (without neonates who died or were transferred)

	P value	Lower 95% CI	Upper 95% CI
birth weight	<,001	-0.0495	-0.041
gestational age	<,001	-0.203	-0.883
female sex	0.7	-0,550	0.777
CC	0.6	-4.605	8.329
CRIB	<,001	0.100	0.687
Apgar 1	0.3	-0.920	0.281
Apgar 5	0.6	-0.435	0.732
choriamnionitis	0.9	-0.936	1.131
PROM	0.8	-0.948	0.696
not less than 1 infection	<,001	-3.074	-1.462

adjusted for birth weight; gestational age; Clinical Risk Index for Babies, CRIB; score, Apgar 1- and 5-minute scores, type of birth, gender, chorioamnionitis, PROM and at least 1 infection.
OR odds ratio; CI confidence interval;
CC Caesarean section; CRIB Critical Risk Index for Babies; LOS length of stay; PROM premature rupture of membranes; VLBW very low birth weight.

The cost estimated in these studies as per person-day of hospitalization in an NICU ranged from 608 to 822 PLN (203 to 274 USD), and the cost per person-day of hospitalization for a neonate with BSI was 2,152 PLN (717 USD). Linking the results obtained in our study concerning the median prolonged LOS of VLBW neonates with BSI and the cost per person-day established by Krawczyk-Wyrwicka, allowed for the estimation of the cost of prolonged LOS in Poland at 12,806 USD; that is, at the upper limit of costs determined by Payne et al.,[30] taking into account multivariate logistic regression, and thus of extension of a shorter stay by about one-third than established in this study.

Rosenthal et al. reported values for prolonged LOS in NICUs similar to those obtained in our present study; for CLABSIs at 18.4 days and for VAP at 25.6 days (based on data from the International Nosocomial Infection Control Consortium and NHSN), but without a cost analysis.[5] Rosenthal et al. also reported a pooled crude mortality rate (undefined) for neonates without infection, at 12.5% and ranging within the limits from 15.2% to 25.3% among neonates with infections. The in-hospital mortality rate of VLBW neonates in our present study was 16.2%.

Analysis of the influence of infection, as conducted in this study, on the LOS among VLBW neonates hospitalized in Polish NICUs revealed a significant correlation between infection and this outcome. However, in order to obtain a worthwhile assessment of this correlation, it is necessary to also assess the general overall condition of the neonate as expressed by such essential parameters as birth weight, gestational age, and CRIB score, which, apart from infection, may also substantially affect the LOS as well as in-hospital mortality (Table 3). A significant correlation between CRIB score, gestational age, and birth weight and the prognosis or treatment outcomes has also been found in other studies [35,36]

5. Conclusions

The general overall condition of VLBW infants statistically increases both mortality and LOS, in contrast to infection, which significantly prolonged only the LOS in the NICU.

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