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Factors associated with inter-institutional variations in sepsis rates of very-low-birth-weight infants in 34 Malaysian neonatal intensive care units

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INTRODUCTION This study aimed to determine whether patient loads, infant status on admission and treatment interventions were significantly associated with inter-institutional variations in sepsis rates in very-low-birth-weight (VLBW) infants in the Malaysian National Neonatal Registry (MNNR).

METHODS This was a retrospective study of 3,880 VLBW (≤ 1,500 g) infants admitted to 34 neonatal intensive care units (NICUs) in the MNNR. Sepsis was diagnosed in symptomatic infants with positive blood culture.

RESULTS Sepsis developed in 623 (16.1%) infants; 61 (9.8%) had early-onset sepsis (EOS) and 562 (90.2%) had late-onset sepsis (LOS). The median EOS rate of all NICUs was 1.0% (interquartile range [IQR] 0%, 2.0%). Compared with NICUs reporting no EOS (n = 14), NICUs reporting EOS (n = 20) had significantly higher patient loads (total live births, admissions, VLBW infants, outborns); more mothers with a history of abortions, and antenatal steroids and intrapartum antibiotic use; more infants requiring resuscitation procedures at birth; higher rates of surfactant therapy, pneumonia and insertion of central venous catheters. The median LOS rate of all NICUs was 14.5% (IQR 7.8%, 19.2%). Compared with NICUs with LOS rates below the first quartile (n = 8), those above the third quartile (n = 8) used less intrapartum antibiotics, and had significantly bigger and more mature infants, more outborns, as well as a higher number of sick infants requiring ventilator support and total parenteral nutrition.

CONCLUSION Patient loads, resuscitation at birth, status of infants on admission and treatment interventions were significantly associated with inter-institutional variations in sepsis.

Keywords: Malaysian, NICU, sepsis, VLBW infants

INTRODUCTION

Neonatal sepsis in very-low-birth-weight (VLBW) infants weighing 1,500 g or less is a common problem in neonatal intensive care units (NICUs), with high morbidity and mortality rates reported in the literature.[1-4] Reports from various neonatal networks showed wide variations in sepsis rates (8.5%–42.0%) among NICUs.[1,5-7] For this study, data was collected from the Malaysian National Neonatal Registry (MNNR), which was established in 2003. One of the MNNR's aims was to improve standards of neonatal care among its NICUs through systematic learning from other units based on evidence. We aimed to determine whether differences in patient loads; demographic, perinatal and patient characteristics; and resuscitation measures at birth were significantly associated with inter-institutional variations in sepsis rates.

METHODS

This was a retrospective study using data from the MNNR, which had a membership of 34 NICUs from Malaysian government hospitals in 2010. The MNNR database was anonymised. Approval for the study was obtained from the National Institutes of Health Malaysia. The inclusion criteria were VLBW infants born between 1 January 2010 and 31 December 2010, either in MNNR hospitals (i.e. inborn) or other facilities (i.e. outborn), and who were admitted to NICUs at these hospitals. The demographic and clinical data of the infants was submitted to the MNNR by trained staff in a standard format. Each infant was a unique case that was not duplicated in the registry, irrespective of the number of times the infant had been admitted to different participating NICUs.

Sepsis was diagnosed in symptomatic infants with a positive blood or cerebrospinal culture. If the infant had confirmed sepsis, data was collected on whether the first episode of sepsis occurred on or before Day 3 of life (early-onset sepsis [EOS]), or after Day 3 of life (late-onset sepsis [LOS]). Data on the following organisms was collected: group B streptococcus (GBS), methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococcus (CoNS), fungus, *Staphylococcus aureus*, *Klebsiella* spp., *Pseudomonas* spp., and *Acinetobacter* spp. Other organisms that were isolated were specified. Gestational assessment was based on the mother's last menstrual period, antenatal ultrasonography or Ballard's score.[8] Infants were classified as appropriate for gestational age (AGA), small for gestational age and large for gestational age when their birth weights were between the 10th and 90th percentile, below the 10th percentile and above the 90th percentile for their gestational age, respectively.[9] Intrapartum antibiotics were administered to the infants' mothers within 24 hours before delivery. Respiratory distress syndrome (RDS) was diagnosed based on clinical and

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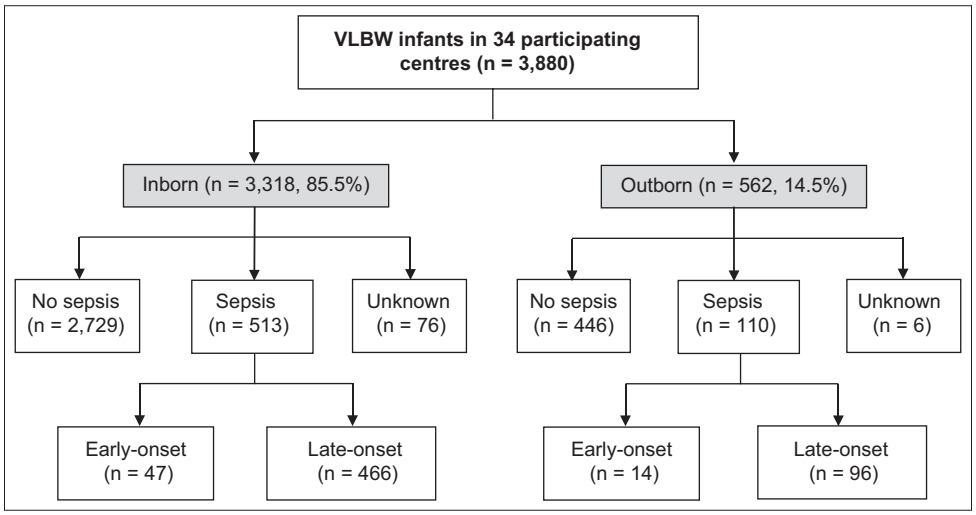

Fig. 1 STROBE diagram shows the details of very-low-birth-weight (VLBW) infants registered in the Malaysian National Neonatal Registry in 2010.

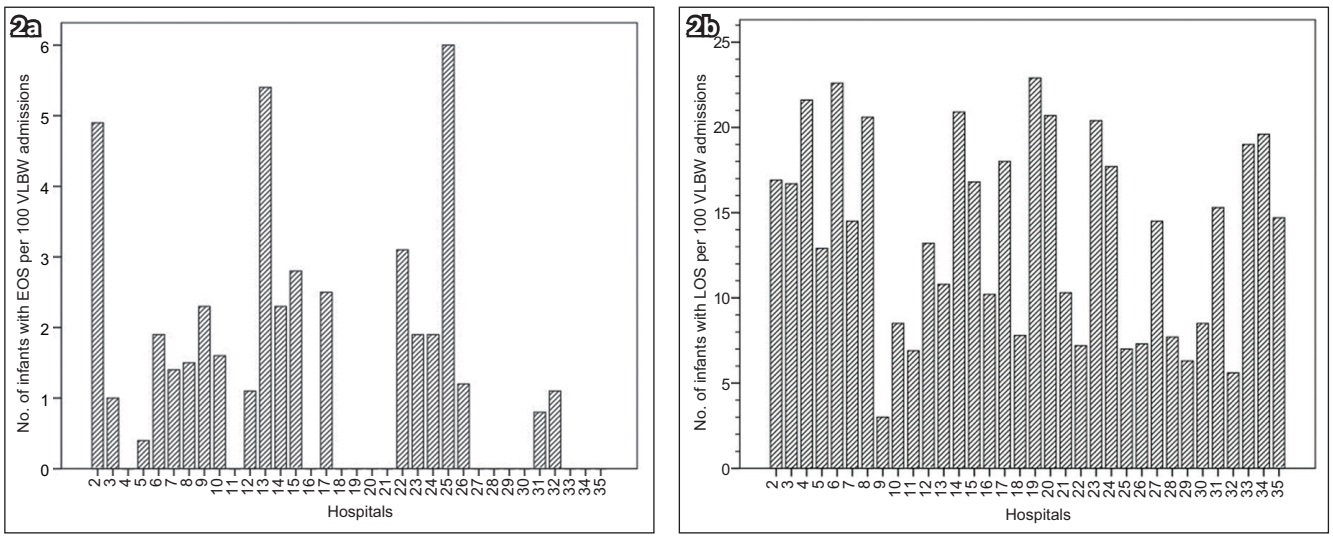

Fig. 2 Bar graphs show (a) early-onset sepsis (EOS) and (b) late-onset sepsis (LOS) rates of very-low-birth-weight (VLBW) infants in 34 neonatal intensive care units in 2010.

chest radiography findings. Necrotising enterocolitis (NEC) was diagnosed based on Stage II or III of Bell's criteria.[10] Patent ductus arteriosus (PDA) was diagnosed based on echocardiographic evidence or the presence of a continuous heart murmur in the left second intercostal space. The central venous catheters used were umbilical, or percutaneously or surgically placed.

Statistical analysis was performed using PASW Statistics version 18.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were reported as mean ± standard deviation for continuous variables with a normal distribution, and median (interquartile range [IQR]) for those with a skewed distribution; categorical variables were reported as frequency and percentage. For comparison between groups in univariate analysis, chi-square test was used for categorical variables, Student's *t*-test for numerical variables with normal distribution and Mann-Whitney *U* test for numerical variables with skewed distributions. For comparison of variables among three groups, the one-way analysis of variance (with Tukey and Games-Howell tests for post hoc analysis, where appropriate) and Kruskal-Wallis test were used for continuous variables, and chi-square test for categorical variables. Logistic regression analysis was performed to identify significant risk factors associated with EOS and LOS in VLBW infants between different groups. Potential risk factors used for logistic regression analysis were variables with p-value < 0.05 identified in the univariate analysis. All tests were two-sided and p-value < 0.05 indicated statistical significance.

RESULTS

The 34 NICUs received a total of 3,880 VLBW infants during the study period (Fig. 1). Sepsis was reported in 623 (16.1%) infants: 61 (9.8%) of these infants had EOS and 562 (90.2%) had LOS. The sepsis status of 82 infants was unknown, including that of 67 infants who died in delivery rooms and six outborns who died shortly after admission.

Fig. 2 shows the EOS and LOS rates of infants in the 34 NICUs. The median EOS rate was 1.0% (IQR 0%, 2.0%; range 0%–6.0%). A total of 14 NICUs did not report any case of EOS, while 20 NICUs reported cases of EOS. The median LOS rate was 14.5% (IQR 7.8%, 19.2%; range 3.0%–22.9%). Eight NICUs had LOS rates below the first quartile (i.e. < 7.8%, low group) with a

Table I. Mortality rates of very-low-birth-weight infants and the causative organisms.

Organism	Early-onset sepsis		Late-onset sepsis	
	Total (n = 61)	Mortality (n = 31)	Total (n = 562)	Mortality (n = 160)
Gram-positive*	31 (50.8)	11 (35.5)	264 (47.0)	53 (20.1)
Bacillus spp.	0	0	10	3 (30.0)
Brevibacterium spp.	0	0	1	0
Corynebacterium spp.	1	0	1	0
Enterococcus spp.	1	0	5	2 (40.0)
Listeria monocytogenes	1	1 (100.0)	0	0
Coagulase-negative staphylococcus	5	0	144	24 (16.7)
Methicillin-resistant *Staphylococcus aureus*	3	2 (66.7)	56	17 (30.4)
S. aureus	4	1 (25.0)	29	5 (17.2)
S. epidermidis	0	0	3	0
Group B streptococcus	16	7 (43.8)	6	2 (33.3)
Group D streptococcus	0	0	5	0
Other Gram-positive bacteria	0	0	4	0
Gram-negative	30 (49.2)	20 (66.7)	298 (53.0)	107 (35.9)
Acinetobacter spp.	10	6 (60.0)	70	23 (32.9)
Burkholderia cepacia	3	1 (33.3)	13	2 (15.4)
Citrobacter spp.	0	0	2	0
Chryseobacterium spp.	0	0	3	1 (33.3)
Enterobacter spp.	2	1 (50.0)	9	7 (77.8)
Escherichia coli	5	4 (80.0)	8	3 (37.5)
Klebsiella spp.	2	2 (100)	83	33 (39.8)
Moraxella spp.	0	0	1	0
Pseudomonas spp.	4	3 (75.0)	49	22 (44.9)
Serratia marcescens	0	0	16	1 (6.3)
Stenotrophomonas maltophilia	0	0	10	6 (60.0)
Other Gram-negative bacteria	4	3 (75.0)	5	0
Fungus	0	0	29	9 (31.0)

Data presented as no. (%). Mortality percentages are calculated using the total number as denominator.

median rate of 7.0% (IQR 5.8%, 7.3%), 18 NICUs had LOS rates between the first and third quartile (intermediate group) with a median LOS rate of 14.5% (IQR 10.3%, 16.8%), and the remaining eight NICUs had rates above the third quartile (high group) with a median LOS rate of 20.8% (IQR 20.5%, 22.4%). Both Gram-positive and -negative organisms were equally common pathogens of EOS and LOS, with GBS (26.2%) being the most common EOS pathogen and CoNS (25.6%) the most common LOS pathogen (Table I). Overall mortality rates were high (191/623, 30.7%).

Table II shows the maternal, perinatal and neonatal variables of all VLBW infants. Compared with infants without sepsis, EOS infants had significantly lower Apgar scores and gestational age, a higher likelihood of being outborn, more morbidities (RDS, pneumonia, NEC), treatment interventions (surfactant therapy, ventilation support, and total parenteral nutrition [TPN]) and types of resuscitation at birth, and a higher mortality rate. Logistic regression analysis showed that, when compared with infants without sepsis, the significant risk factors associated with EOS infants were gestational age (adjusted odds ratio [OR] 0.871, 95% confidence interval [CI] 0.790, 0.961; p = 0.006), endotracheal tube (ETT) ventilation at birth (adjusted OR 2.651, 95% CI 1.367, 5.143; p = 0.004) and pneumonia (adjusted OR 2.141, 95% CI 1.163, 3.940; p = 0.014). Apgar scores, bag-and-mask ventilation and adrenaline therapy at birth, being outborn, surfactant therapy, NEC, conventional ventilation, high frequency oscillatory ventilation (HFOV), TPN and the use of a central venous catheter were not significant risk factors.

Compared with infants without sepsis (Table II), LOS infants had significantly higher rates of spontaneous vertex delivery (SVD), more resuscitation at birth, lower birth weight and gestational age, a higher likelihood of being AGA and outborn, lower admission temperatures, more clinical problems and treatment interventions, and a longer duration of hospital stay. Logistic regression analysis showed that, when compared with infants without sepsis, the significant risk factors associated with LOS infants were SVD (adjusted OR 1.414, 95% CI 1.163, 1.718; p = 0.001), birth weight (adjusted OR 0.999, 95% CI 0.999, 1.000; p = 0.002), pneumonia (adjusted OR 1.974, 95% CI 1.483, 2.330; p < 0.0001), PDA (adjusted OR 1.974, 95% CI 1.610, 2.419; p < 0.0001), NEC (adjusted OR 2.267, 95% CI 1.688, 3.044; p < 0.0001), continuous positive airway pressure (CPAP) therapy (adjusted OR 1.351, 95% CI 1.109, 1.647; p = 0.003), conventional ventilation (adjusted OR 1.742, 95% CI 1.348, 2.251; p < 0.0001) and TPN (adjusted OR 2.413, 95% CI 1.904, 3.059; p < 0.0001). Oxygen therapy, resuscitation at birth with bag-and-mask or ETT ventilation, gestational age, growth status

Table II. Comparison of maternal, perinatal and neonatal variables of very-low-birth-weight infants with and without sepsis.

Variable	No. (%)				
	Total (n = 3,880)	No sepsis (n = 3,175)	EOS (n = 61)	LOS (n = 562)	Unknown (n = 82)
Maternal					
Age (yr)*	28 (24, 33) (n = 3,877)	38 (24, 33) (n = 3,877)	28 (25, 30) (n = 61)	28 (23, 33) (n = 560)	30 (25, 36) (n = 82)
Gravida*	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 5)
Parity*	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 3)
Ethnic group					
Malay	2,393 (61.7)	1,973 (62.1)	46 (75.4)	331 (58.9)	43 (52.4)
Chinese	349 (9.0)	283 (8.9)	4 (6.6)	56 (10.0)	6 (7.3)
Indian	264 (6.8)	203 (6.4)	2 (3.3)	44 (7.8)	15 (18.3)
Sabahan	218 (5.6)	179 (5.6)	1 (1.6)	28 (5.0)	10 (12.2)
Sarawakian	311 (8.0)	254 (8.0)	4 (6.6)	53 (9.4)	0
Other	100 (2.6)	83 (2.6)	0	13 (2.3)	4 (4.9)
Foreigner	245 (6.3)	200 (6.3)	4 (6.6)	37 (6.6)	4 (4.9)
Previous abortion	739 (19.0)	608 (19.1)	9 (14.8)	96 (17.1)	26 (31.7)
Diabetes mellitus	485/3,697 (13.1)	396/3,030 (13.1)	9/59 (15.3)	62/532 (11.7)	18/76 (23.7)
Hypertension	907/3,704 (24.5)	778/3,037 (25.6)	9/60 (15.0)	110/531 (20.7)	10/76 (13.2)
Chorioamnionitis	166/3,692 (4.5)	131/3,027 (4.3)	4/59 (6.8)	26/531 (4.9)	5/75 (6.7)
Intrapartum antibiotics	726/3,737 (19.4)	576/3,061 (18.8)	13/59 (22.0)	126/536 (23.5)	11/81 (13.6)
Antenatal steroid	2,419/3,736 (64.7)	1,984/3,057 (64.9)	31/60 (51.7)	381/540 (70.6)	23/79 (29.1)
Mode of delivery					
SVD	2,019 (52.0)	1,578 (49.7)	41 (67.2)	327 (58.2)§	73 (89.0)
Instrumental	10 (0.3)	9 (0.3)	0	1 (0.2)	0
LSCS	1,850 (47.7)	1,587 (50.0)	20 (32.8)	234 (41.6)	9 (11.0)
Unknown	1 (0.03)	1 (0.03)	0	0	0
Infant					
Female	1,783 (46.0)	1,448 (45.6)	22 (36.1)	270 (48.0)	43 (52.4)
Outborn	562 (14.5)	446 (14.0)	14 (23.0)‡	96 (17.1)‡	6 (7.3)
Singleton	3,304 (85.2)	2,685 (84.6)	54 (88.5)	497 (88.4)	68 (82.9)
Apgar score*					
At 1 min	7 (5, 9) (n = 3,669)	7 (5, 9) (n = 3,005)	6 (3, 8)‡ (n = 56)	7 (5, 8) (n = 536)	2 (1, 3) (n = 72)
At 5 min	9 (7, 9) (n = 3,424)	9 (5, 9) (n = 2,818)	8 (5.8, 9.0)§ (n = 54)	9 (7, 9) (n = 493)	1 (1, 3) (n = 59)
Resuscitation at birth					
Oxygen	3,112 (80.2)	2,540 (80.0)	53 (86.9)	489 (87.0)¶	30 (36.6)
Bag-and-mask ventilation	2,218 (57.2)	1,775 (55.9)	46 (75.4)§	384 (68.3)¶	13 (15.9)
Chest compression	149 (3.8)	121 (3.8)	5 (8.2)	14 (2.5)	9 (11.0)
ETT ventilation	2,065 (53.2)	1,625 (51.2)	47 (77.0)¶	383 (68.1)¶	10 (12.2)
Adrenaline	101 (2.6)	81 (2.6)	5 (8.2)‡	7 (1.2)	8 (9.8)
Birth weight* (g)	1,160 (930, 1,350)	1,190 (960, 1,370)	1,150 (925, 1,335)	1,055 (874, 1,250)¶	611 (554, 898)
Gestation† (wk)	29.5 ± 3.1	29.8 ± 3.1	28.4 ± 2.6¶	28.1 ± 2.6¶	26.3 ± 3.7
Intrauterine growth status					
AGA	2,366 (61.0)	1,894 (59.7)	38 (62.3)	383 (68.1)§	51 (62.2)
LGA	82 (2.1)	68 (2.1)	1 (1.6)	12 (2.1)	1 (1.2)
SGA	1,432 (36.9)	1,213 (38.2)	22 (36.1)	167 (29.7)	30 (36.6)
Admission temperature* (°C)	36.0 (35.2, 36.5)	36.5 (36.0, 36.8)	36.0 (35.2, 36.5)	36.0 (35.0, 36.5)¶	35.5 (35.0, 36.0) (n = 25)
RDS	2,844/3,798 (74.9)	2,298 (72.4)	54 (88.5)§	492 (87.5)¶	–
Surfactant therapy	2,259/3,798 (59.5)	1,792 (56.4)	49 (80.3)¶	418 (74.4)¶	0
Pneumonia	630 (16.2)	459 (14.5)	16 (26.2)‡	155 (27.6)¶	0
PDA	931 (24.0)	659 (20.8)	18 (29.5)	254 (45.2)¶	0

(*Contd*...)

Variable	No. (%)				
	Total (n = 3,880)	No sepsis (n = 3,175)	EOS (n = 61)	LOS (n = 562)	Unknown (n = 82)
NEC	262 (6.8)	162 (5.1)	7 (11.5)‡	93 (16.5)¶	0
Major congenital anomalies	295 (7.6)	235 (7.4)	5 (8.2)	55 (9.8)	0
CPAP	1,653 (42.6)	1,331 (41.9)	24 (39.3)	298 (53.0)¶	0
Conventional ventilation	2,501 (64.5)	1,981 (62.4)	50 (82.0)§	470 (83.6)¶	0
HFOV	261 (6.7)	195 (6.1)	11 (18.0)§	55 (9.8)§	0
TPN	1,961 (50.5)	1,480 (46.6)	41 (67.2)§	440 (78.3)¶	0
CVC use	2,322 (59.8)	1,835 (57.8)	47 (77.0)‡	440 (78.3)¶	0
Death	1,037 (26.7)	846 (26.6)	31 (50.8)¶	160 (28.5)	82 (100.0)
Duration of hospital stay* (day)					
Total	35 (15, 56)	34 (15, 53)	27 (3, 56)	54 (32, 79)¶	0
Survivors	44.0 (31.0, 63.0) (n = 2,843)	42.0 (30.0, 59.0) (n = 2,411)	49.0 (32.0, 73.5) (n = 30)	61.5 (45.0, 86.0)¶ (n = 402)	–

Value of n provided for variables with missing data. *Data presented as median (interquartile range). †Data presented as mean ± standard deviation. Statistically significant at ‡$p < 0.05$, §$p < 0.001$, ¶$p < 0.0001$ compared to infants without sepsis. AGA: appropriate for gestational age; CPAP: continuous positive airway pressure; CVC: central venous catheter; ETT: endotracheal tube; HFOV: high frequency oscillatory ventilation; LGA: large for gestational age; LSCS: lower segment Caesarean section; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome; SGA: small for gestational age; SVD: spontaneous vertex delivery; TPN: total parenteral nutrition

Table III. Comparison of patient loads of Malaysian neonatal intensive care units (NICUs) with and without early-onset sepsis (EOS) in infants with very low birth weight (VLBW) and extremely low birth weight (ELBW).

Variable	Median (interquartile range)		p-value*
	NICUs without EOS (n = 14)	NICUs with EOS (n = 20)	
Live births per NICU	4,955 (3,900, 6,392)	9,947 (7,553, 11,982)	< 0.0001
Admissions per NICU			
Total	1,418 (774, 2,033)	2,899 (2,235, 3,898)	0.001
VLBW (≤ 1,500 g)	55 (45, 83)	130 (98, 208)	< 0.0001
ELBW (< 1,000 g)	17 (12, 23)	42 (28, 61)	< 0.0001

*Statistically significant at $p < 0.05$.

at birth, being outborn, admission temperature, RDS, surfactant therapy, HFOV and use of a central venous catheter were not significant risk factors.

There were no significant differences in maternal, intrapartum and neonatal variables (Table II) between EOS and LOS infants, except that EOS infants had significantly lower Apgar scores at one minute ($p = 0.037$) and five minutes ($p = 0.023$) of life, more chest compression ($p = 0.030$) and adrenaline therapy ($p = 0.004$) at birth, and a higher mortality rate ($p < 0.0001$). LOS infants had a significantly higher rate of exposure to antenatal steroids ($p = 0.007$), lower admission temperature ($p = 0.013$), more PDA ($p = 0.019$) and CPAP therapy ($p = 0.042$), less HFOV ($p = 0.047$), and a longer duration of hospital stay ($p < 0.0001$) among the survivors ($p = 0.030$).

Tables III and IV show a comparison of the patient loads and characteristics of VLBW infants in NICUs with and without EOS. Compared with NICUs without EOS infants, those with EOS infants had significantly more live births, admissions, VLBW and extremely-low-birth-weight (ELBW) infants, and outborns. Furthermore, in these NICUs, a significantly higher proportion of mothers of VLBW infants had a history of abortion and use of antenatal steroids or intrapartum antibiotics; the infants had lower birth weight and gestational age; there were also more infants requiring bag-and-mask ventilation, chest compression, ETT ventilation and adrenaline at birth, as well as higher incidences of surfactant therapy, pneumonia and insertion of central venous catheters.

Tables V and VI show a comparison of the patient loads and variables of NICUs with low, intermediate and high LOS rates. There was no significant difference in total, VLBW and ELBW admissions to the NICU among these three groups. When compared with VLBW infants in NICUs with low LOS rates, those in NICUs with high LOS rates had significantly younger mothers ($p < 0.001$), higher birth weight ($p < 0.001$) and gestational age ($p = 0.027$), a higher likelihood of being AGA ($p < 0.0001$), outborn ($p = 0.033$) and singleton ($p = 0.015$), lower Apgar score at one minute of life ($p < 0.001$), and were more likely to require oxygen therapy ($p = 0.002$), bag-and-mask ventilation ($p < 0.001$) and ETT ventilation ($p = 0.011$) at birth. Such infants also had lower admission temperature ($p = 0.017$), more RDS ($p < 0.001$), surfactant therapy ($p < 0.001$), pneumonia ($p < 0.001$) and PDA ($p < 0.001$), used less intrapartum antibiotics ($p = 0.038$), and received more conventional mechanical ventilation ($p = 0.034$) and TPN ($p < 0.001$).

Table IV. Comparison of maternal, perinatal and neonatal variables in very-low-birth-weight infants in Malaysian neonatal intensive care units (NICUs) with and without early-onset sepsis (EOS).

Variable	No. (%)		p-value
	NICUs without EOS (n = 970)	NICUs with EOS (n = 2,910)	
Maternal			
Age* (yr)	28 (23, 33)	28 (24, 33)	0.073
Gravida*	2 (1, 4)	2 (1, 3)	0.238
Parity*	1 (0, 2)	1 (0, 2)	0.659
Previous abortion	163 (16.8)	576 (19.8)	0.040‡
Diabetes mellitus	128/914 (14.0)	357/2,783 (12.8)	0.361
Hypertension	227/915 (24.8)	680/2,789 (24.4)	0.794
Chorioamnionitis	50/917 (5.5)	116/2,775 (4.2)	0.107
Antenatal steroid	592/955 (62.0)	1,827/2,781 (65.7)	0.039‡
Intrapartum antibiotics	162/944 (17.2)	564/2,793 (20.2)	0.042‡
Infant			
Female	438 (45.2)	1,345 (46.2)	0.831
Outborn	115 (11.9)	447 (15.4)	0.007‡
Singleton	838 (86.4)	2,466 (84.7)	0.211
Birth weight* (g)	1,180 (940, 1,459)	1,150 (925, 1,350)	0.039‡
Gestation* (wk)	30 (27, 32)	29 (27, 31)	0.021‡
Intrauterine growth status			0.579
AGA	605 (62.4)	1,761 (60.5)	
LGA	19 (2.0)	63 (2.2)	
SGA	346 (35.7)	1,086 (37.3)	
LSCS delivery	451 (46.5)	1,399 (48.1)	0.742
Apgar score*			
At 1 min	7 (5, 9) (n = 922)	7 (5, 9) (n = 2,747)	0.194
At 5 min	9 (8, 9) (n = 856)	9 (7, 9) (n = 2,568)	0.667
Resuscitation at birth			
Oxygen	785 (80.9)	2,327 (80.0)	0.515
Bag-and-mask ventilation	498 (51.3)	1,720 (59.1)	< 0.0001‡
Chest compression	20 (2.1)	129 (4.4)	0.001‡
ETT ventilation	468 (48.2)	1,597 (54.9)	< 0.0001‡
Adrenaline	11 (1.1)	90 (3.1)	0.001‡
Admission temperature† (ºC)	35.80 ± 0.98 (n = 959)	35.80 ± 1.06 (n = 2,864)	0.072
Respiratory distress syndrome	710/955 (74.3)	2,134/2,843 (75.1)	0.659
Surfactant therapy	541/955 (56.6)	1,718/2,843 (60.4)	0.04‡
Pneumonia	115 (11.9)	515 (17.7)	< 0.0001‡
Central venous catheter use	533/951 (56.0)	1,789/2,813 (63.6)	< 0.0001‡

Value of n provided for variables with missing data. *Data presented as median (interquartile range). †Data presented as mean ± standard deviation. ‡Statistically significant at p < 0.05. AGA: appropriate for gestational age; ETT: endotracheal tube; LGA: large for gestational age; LSCS: lower segment Caesarean section; SGA: small for gestational age

Table V. Comparison of patient loads of Malaysian neonatal intensive care units (NICUs) with differing late-onset sepsis (LOS) rates in very-low-birth-weight (VLBW) infants.

Variable	Median (interquartile range)			p-value
	Low LOS* (n = 8)	Intermediate LOS† (n = 18)	High LOS‡ (n = 8)	
Live births per NICU	8,826 (4,752, 10,209)	7,592 (5,026, 10,424)	5,853 (4,875, 12,221)	0.931
Admissions per NICU				
Total	2,945 (2,247, 4,566)	2,065 (1,494, 3,190)	1,369 (931, 4,461)	0.310
VLBW (≤ 1,500 g)	97 (52, 124)	113 (69, 208)	95 (51, 197)	0.655
ELBW (< 1,000 g)	29 (14, 50)	28 (22, 58)	29 (14, 50)	0.739

LOS rate *< 7.8%, †≥ 7.8% and < 19.2%, ‡≥ 19.2%. ELBW: extremely low birth weight

Table VI. Comparison of maternal, perinatal and neonatal variables in Malaysian neonatal intensive care units with differing late-onset sepsis (LOS) rates in very-low-birth-weight infants.

Variable	No. (%)			p-value
	Low LOS* (n = 746)	Intermediate LOS† (n = 2,216)	High LOS‡ (n = 918)	
Maternal				
Age§ (yr)	29.3 ± 6.5	28.7 ± 6.5	27.9 ± 7.1	< 0.001‖
Gravida¶	2 (1, 4)	2 (1, 3)	2 (1, 4)	0.075
Parity¶	1 (0, 2)	1 (0,2)	1 (0, 2)	0.063
Diabetes mellitus	92/716 (12.8)	275/2,102 (13.1)	118/879 (13.4)	0.942
Hypertension	159/716 (22.2)	532/2,107 (25.2)	216/881 (24.5)	0.262
Chorioamnionitis	28/717 (3.9)	104/2,095 (5.0)	34/880 (3.9)	0.291
Antenatal steroid	447/726 (61.6)	1,380/2,107 (65.5)	592/903 (65.6)	0.136
Intrapartum antibiotics	169/724 (23.3)	385/2,114 (18.2)	172/899 (19.1)	0.010‖
Infant				
Female	343 (46.0)	1,011 (45.6)	429 (46.7)	0.977
Outborn	81 (10.9)	349 (15.7)	132 (14.4)	0.005‖
Singleton	621 (83.2)	1,880 (84.8)	803 (87.5)	0.044‖
Birth weight§ (g)	1,102 ± 274	1,119 ± 267	1,148 ± 266	0.001‖
Gestation§ (wk)	29.4 ± 3.1	29.5 ± 3.1	29.8 ± 3.1	0.028‖
Intrauterine growth status				
AGA	395 (52.9)	1,358 (61.3)	613 (66.8)	< 0.001‖
LGA	16 (2.1)	41 (1.9)	25 (2.7)	0.055
SGA	335 (44.9)	817 (36.9)	280 (30.5)	Reference
LSCS delivery	346 (46.4)	1,099 (49.6)	405 (44.1)	0.100
Apgar score¶				
At 1 min	8 (5, 9) (n = 715)	7 (5,8) (n = 2,082)	7 (5,8) (n = 872)	< 0.001‖
At 5 min	9 (7,9) (n = 662)	9 (7,9) (n = 1,967)	9 (8,9) (n = 795)	0.102
Resuscitation at birth				
Oxygen	575 (77.1)	1,775 (80.1)	762 (83.0)	0.010‖
Bag-and-mask ventilation	379 (50.8)	1,289 (58.2)	550 (59.9)	< 0.001‖
Chest compression	21 (2.8)	84 (3.8)	44 (4.8)	0.11
Endotracheal tube ventilation	370 (49.6)	1,182 (53.3)	513 (55.9)	0.038‖
Adrenaline	14 (1.9)	66 (3.0)	21 (2.3)	0.208
Admission temperature¶ (ºC)	36.2 (35.9, 36.5) (n = 731)	36.0 (35.0, 36.5) (n = 2,177)	36.1 (35.3, 36.5) (n = 915)	< 0.001‖
RDS	527/722 (73.0)	1,596/2,165 (73.7)	721/911 (79.1)	0.003‖
Surfactant therapy	380/722 (52.6)	1,287/2,165 (59.4)	592/911 (65.0)	< 0.001‖
Pneumonia	67 (9.0)	425 (19.2)	138 (15.0)	< 0.001‖
PDA	158/722 (21.9)	498/2,165 (23.0)	275/911 (30.2)	< 0.001‖
Necrotising enterocolitis	40/722 (5.5)	172/2,165 (7.9)	50/911 (5.5)	0.014‖
CPAP	254/746 (34.0)	1,053/2,216 (47.5)	346/918 (37.7)	< 0.001‖
Conventional ventilation	481 (64.5)	1,383 (62.4)	637 (69.4)	0.001‖
HFOV	63 (8.4)	141 (6.4)	57 (6.2)	0.112
Total parenteral nutrition	335/722 (46.4)	1,096/2,165 (50.6)	530/911 (58.2)	< 0.001‖
Central venous catheter use	460/715 (64.3)	1,288/2,141 (60.2)	574/908 (63.2)	0.077

LOS rate *< 7.8%, †≥ 7.8 and < 19.2, ‡≥ 19.2%. §Data presented as mean ± standard deviation. ¶Data presented as median (interquartile range). ‖Statistically significant p < 0.05. AGA: appropriate for gestational age; CPAP: continuous positive airway pressure; HFOV: high frequency oscillatory ventilation; LGA: large for gestational age; LSCS: lower segment Caesarean section; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome; SGA: small for gestational age

DISCUSSION

This study showed that EOS was not common in Malaysian VLBW infants, but that it had a high mortality rate. The EOS and LOS rates of Malaysian NICUs were comparable with those of some networks/registries,[3,11] but lower than the rates reported by others.[12,13]

Unlike reports in which Gram-negative organisms were the predominant pathogens[3,11,14-16] both Gram-positive

and -negative organisms were common EOS pathogens in Malaysian VLBW infants. GBS, the most common pathogen of EOS in our NICUs, produced a higher mortality rate than in other reports.[11,17] Multivariate analysis showed that lower gestational age, resuscitation at birth with ETT ventilation and pneumonia were the only significant risk factors associated with EOS among VLBW infants, compared to those without EOS. Stoll et al have proposed that ascending amniotic infections by maternal vaginal flora are responsible for most cases of EOS.[15] In the present study, we suspect that chorioamnionitis was underreported, as almost a quarter of EOS infants received intrapartum antibiotics.[18] Intrapartum antibiotics have been reported to be effective in the prevention and treatment of chorioamnionitis.[15] Similar to Klinger et al,[18] we found that delivery room ETT ventilation was a significant risk factor for EOS. Compromise of respiratory mucosa due to endotracheal intubation and contamination of the ETT during resuscitation were possible underlying mechanisms of EOS and pneumonia.

Some networks have found that Gram-positive organisms were the most common pathogens of LOS.[1-3,11,12,16,19,20] However, in the current study, both Gram-positive and -negative organisms were found to be common pathogens of LOS, with CoNS being the most common Gram-positive pathogen in Malaysian NICUs. Unlike NICUs in other countries,[1,11,19-21] *Escherichia coli* was not found to be the most common Gram-negative LOS pathogen in Malaysian NICUs in our study. Fungal infection was also less common (4.7%) than in other networks/registries, which reported an incidence of more than 10.0%.[1,11,12,19,20,22] In our study, multivariate analysis showed that, when compared with VLBW infants without LOS, the significant risk factors associated with VLBW infants with LOS were lower birth weight, SVD, pneumonia, PDA, NEC, CPAP therapy, conventional ventilation and TPN.

This study also showed that there were differences between EOS and LOS infants. EOS infants had significantly lower Apgar scores, hence requiring more extensive resuscitation procedures at birth than LOS infants. However, LOS infants had significantly higher rates of exposure to antenatal steroids, lower admission temperature, more PDA and higher rates of respiratory support. A possible mechanism underlying the increased risk of LOS is the suppression of the immature immune system by antenatal steroids. Generally, infants with hypothermia and PDA necessitated more intervention and a longer duration of respiratory support, which could subsequently contribute to sepsis.

Similar to the findings in other networks,[1,5-7] we also observed a wide variability in sepsis rates. When compared with Malaysian NICUs that reported no EOS in their VLBW infants, those with reported EOS in their VLBW infants had significantly higher patient loads (number of live births, admissions, VLBW and ELBW infants, outborn infants) and more therapeutic interventions at birth (resuscitation procedures, surfactant therapy and insertion of CVCs). Furthermore, they had a significantly larger number of mothers with a previous history of abortions and use of intrapartum antibiotics, suggesting that intrapartum infections were more common among populations giving birth to VLBW infants served by these NICUs. Unfortunately, data on prolonged rupture of membranes and maternal intrapartum fever were not available in the MNNR database. When compared with NICUs with low LOS rates, those with high LOS rates had bigger, more mature infants, more outborn infants, and used less intrapartum antibiotics. These NICUs also had significantly more sick infants (lower one-minute Apgar scores, more resuscitation at birth, lower admission temperature, more RDS, pneumonia and PDA) who required more ventilator support and TPN, which increased their risk of LOS.

A literature review showed that no studies have reported on the association of these risk factors with inter-institutional variability. Our findings suggest that when comparing outcomes of infection control strategies among different NICUs, the factors listed are potential confounders. Therefore, the ability to cope with higher patient loads and improvement of standards of perinatal care are issues that need to be addressed concomitantly when undertaking evidence-based preventive strategies to reduce sepsis rates in Malaysian NICUs.

The limitations of this study include: possible underreporting of LOS, as only the first episode of sepsis was entered in the database; lack of data on the incidence of prolonged rupture of membranes and maternal intrapartum fever; and lack of data on the duration of CVC use, which could be a significant factor associated with inter-institutional variations in sepsis rates.

In conclusion, the current study found that patient loads, patient characteristics and perinatal interventions were significant factors associated with inter-institutional variations of sepsis rates in Malaysian NICUs.

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