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# ORIGINAL ARTICLE

## Early-onset sepsis in Malaysian neonatal intensive care units

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*Abstract*

Objectives: To determine the incidence, causative pathogens, morbidities, mortality, and risk factors associated with blood culture-positive early-onset sepsis (EOS, ≤72 hours of age) in symptomatic neonates admitted to the neonatal intensive care units (NICUs) of a middle-income country. Study Design: Retrospective cohort study using data submitted prospectively to the Malaysian National Neonatal Registry (MNNR). Setting: 44 Malaysian NICUs. Participants: All neonates born in 2015-2020. Results: EOS was reported in 991 neonates. The annual incidence of EOS increased from 0.46 to 0.49/1000 livebirths over the six years. The most common pathogen was *Streptococcus agalactiae* or Group B haemolytic streptococcus (GBS) (n=388, 39.2%), followed by *Escherichia coli* (*E. coli*) (n=80, 8.1%), Klebsiella spp (n=73, 7.4%), coagulase negative staphylococcus (CONS) (n=73, 7.4%), Pseudomonas spp (n=44, 4.4%) and methicillin-sensitive *Staphylococcus aureus* (n=34, 3.4%). The incidence of EOS due to GBS increased from 0.17 to 0.22/1000 livebirths. Morbidities and mortality were higher in those with EOS than without EOS. Multiple logistic regression analysis showed that Indian ethnic group, chorioamnionitis, gestation≥37weeks, female, spontaneous vaginal delivery, instrumental delivery, and surfactant therapy were significantly associated with increased risk of EOS due to GBS. Four factors were significantly associated with increased risk of non-GBS EOS (outborns, birthweight <1000 g, vaginal delivery, and surfactant therapy). Early continuous positive airway pressure was associated with significantly lower risk of EOS. Conclusion: The incidence of EOS showed an increasing trend in Malaysian NICUs. GBS was the most common causative pathogen. Several modifiable risk factors associated with EOS have been identified.

*Keywords:* Early-onset sepsis, neonatal intensive care units, Malaysia, group B haemolytic streptococci, early CPAP, surfactant therapy

### INTRODUCTION

Early-onset sepsis (EOS), defined as blood culture-positive infection in symptomatic neonates within the first 72 hours of life, has been widely recognised as a significant cause of morbidities and mortality in neonatal intensive care units (NICUs) worldwide.[1-4] EOS is usually due to vertical transmission occurring *in utero,* during delivery, or after delivery. The mechanisms of *in utero* transmission is due to prolonged rupture of membrane or during labour when organisms in the birth canal enter through the amniotic membranes causing chorioamnionitis, or the foetus becomes infected by swallowing or inhaling infected amniotic fluid. During birth, a neonate may become infected as it passes through the birth canal. After birth, it may be infected via breaches in its skin or mucus membrane which has been colonised by organisms acquired perinatally.

Given the high morbidities and mortalities associated with EOS, understanding the epidemiology of EOS in each country is of paramount importance to help strategise and

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implement appropriate preventive measures to reduce the burden of this condition. To date, national epidemiology studies of EOS were reported primarily from high-income countries (HICs),[1-8] and none from low- and middle-income countries (LMICs). The objectives of the present study were to determine the incidence, causative pathogens, morbidities, mortality, and risk factors associated with microbiologically culture-positive EOS in NICUs in Malaysia, a middle-income country.

## MATERIALS AND METHODS

This was a retrospective cohort study of neonates born in years 2015-2020 in 44 Malaysian NICUs participating in the Malaysian National Neonatal Registry (MNNR). Data of neonates were collected prospectively in a standardised format by trained health personnel and submitted to the MNNR. The inclusion criteria for neonates in the MNNR were very low birthweight (VLBW, <1500g) or very preterm (VP, <32 weeks) gestation, those with culture-positive sepsis in blood and/or CSF, late preterm/term neonates (≥35 weeks) with hypoxic-ischaemic encephalopathy, on respiratory support, death before discharge, or congenital heart diseases (from 2017). All data were anonymised. Data of neonates admitted multiple times were merged before analysis.

*Definitions*

Gestation was reported in completed weeks based on antenatal ultrasound findings, or maternal last menstrual period, or the New Ballard scores.[9] Antenatal steroids were any administration of steroids before birth. Outborns were neonates transferred-in to a participating centre. Early continuous positive pressure (eCPAP) therapy was defined as receiving CPAP in delivery rooms shortly after birth. EOS was diagnosed in symptomatic neonates with positive blood culture at ≤72 hours of life. Necrotising enterocolitis (NEC) was diagnosed based on presence of Bell's stage 2 or 3 changes.[10] Chorioamnionitis was diagnosed by obstetric doctors in the presence of maternal fever (≥38.0°C) and any of the following two criteria: maternal tachycardia (>100 beats/minute), foetal tachycardia (>160 beats/minute), leucocytosis ($15x10^8$/L), raised C-reactive protein, uterine tenderness, foul-smelling liquor.

*Ethics approval*

Parental consent was not obtained for this study as the database was anonymised. Ethical clearance for the study was granted by the Malaysian Ministry of Health and registered under the National Medical Research Registry (NMRR-05-04-168).

*Statistical analysis*

The SPSS version 28.0 (IBM) was used for statistical analysis. The incidence of EOS of inborn neonates per 1000 livebirths in the participating hospitals was calculated for each year. We compared maternal and neonatal demographic and clinical data between neonates with and without EOS, and among neonates with EOS due to GBS (GBS EOS), EOS due to non-GBS pathogens (non-GBS EOS) and without EOS of all gestations and birthweights, and in the very low birthweight (<1500g, VLBW) neonates. The Chi Square test was used for analysis of categorical variables and Student t test for continuous variables with normal distributions. Association of predetermined independent factors with EOS due to GBS and with non-GBS EOS were investigated using multiple logistic regression models, respectively. These factors were: maternal age, maternal parity, ethnic groups, maternal diabetes mellitus, chorioamnionitis, antenatal steroids, intrapartum antibiotics, inborn/outborn, birthweight, gestation, intrauterine growth status, gender, modes of delivery, and procedures received shortly after birth (eCPAP, bag-and-mask ventilation, endotracheal intubation, and surfactant therapy). Multicollinearity of independent factors were checked by calculating the variance inflection factors (VIF). Factors with VIF>4 were removed from final analysis. P values of <0.05 were considered statistically significant.

## RESULTS

*Epidemiology*

During these six years, there were 1,791,968 livebirths delivered in the participating hospitals. A total of 98355 neonates (both inborns and outborns) admitted to these hospitals met the inclusion criteria of the MNNR. Table 1 shows their demographic characteristics. More than two-thirds of them had birthweight ≥1500g and gestation ≥32 weeks, and were appropriate for gestational age, Malays and inborns. Of the 98355 neonates, 726 (0.7%) did not have data on EOS status (yes/no). We present here the findings of 97629 (99.3%) neonates with EOS data.

EOS was reported in 991/97629 (1.0%)

**Table 1: Demographic characteristics of all neonates in the Malaysian National Neonatal Database, 2015-2020**

| Variables | Number of neonates N=98355 (%) |
|---|---|
| Mean birthweight, g (±SD) | 2316 (884) |
| Birthweight groups, g | |
| <1000 | 6513 (6.6) |
| 1000-1499 | 14623 (14.9) |
| 1500-2499 | 32635 (33.2) |
| ≥2500 | 44584 (45.3) |
| Gestation, weeks | |
| <28 | 5275 (5.4) |
| 28 to <32 | 14781 (15.0) |
| 32 to <37 | 34114 (34.7) |
| ≥37 | 44185 (44.9) |
| Intrauterine growth categories | |
| AGA | 68707 (69.9) |
| SGA | 24668 (25.1) |
| LGA | 4980 (5.1) |
| Ethnic groups | N=98325 |
| Malay | 66499 (67.6) |
| Chinese | 7270 (7.4) |
| Indians | 5947 (6.0) |
| Sabah Indigenous people | 5285 (5.4) |
| Sarawak Indigenous people | 4430 (4.5) |
| Orang Asli | 1220 (1.2) |
| Other Malaysian | 547 (0.6) |
| Foreigners | 7127 (7.2) |
| Gender | |
| Male | 57697 (58.7) |
| Female | 40460 (41.1) |
| Indeterminate | 169 (0.17) |
| Unknown | 29 (0.03) |
| Place of birth | |
| Inborn | 88299 (89.8) |
| Outborn | 10053 (10.2) |
| Unknown | 3 (0.0) |

Note: AGA, appropriate-for-gestational age; SGA, small-for-gestational age; LGA, large-for-gestational age; SD, standard deviation.

neonates. Figure 1 shows the most common pathogen was *Streptococcus agalactiae* or Group B haemolytic streptococcus (GBS) (n=388, 39.2%), followed by *Escherichia coli* (*E. coli*) (n=80, 8.1%), Klebsiella spp (n=73, 7.4%), coagulase negative staphylococcus (CONS) (n=73, 7.4%), Pseudomonas spp (n=44, 4.4%) and methicillin-sensitive *Staphylococcus aureus* (n=34, 3.4%). *Listeria monocytogenes* was very uncommon (n=8, 0.8%). In VLBW neonates with EOS (Fig. 2), GBS was the most common (n=76, 22.6%), followed by CONS (n=43, 12.8%), *E. coli* (n=33, 9.8%), Klebsiella spp., (n=33, 9.8%), and pseudomonas spp. (n=21, 6.2%). In extremely low birthweight (ELBW, <1000g) neonates with EOS, GBS (n=34,

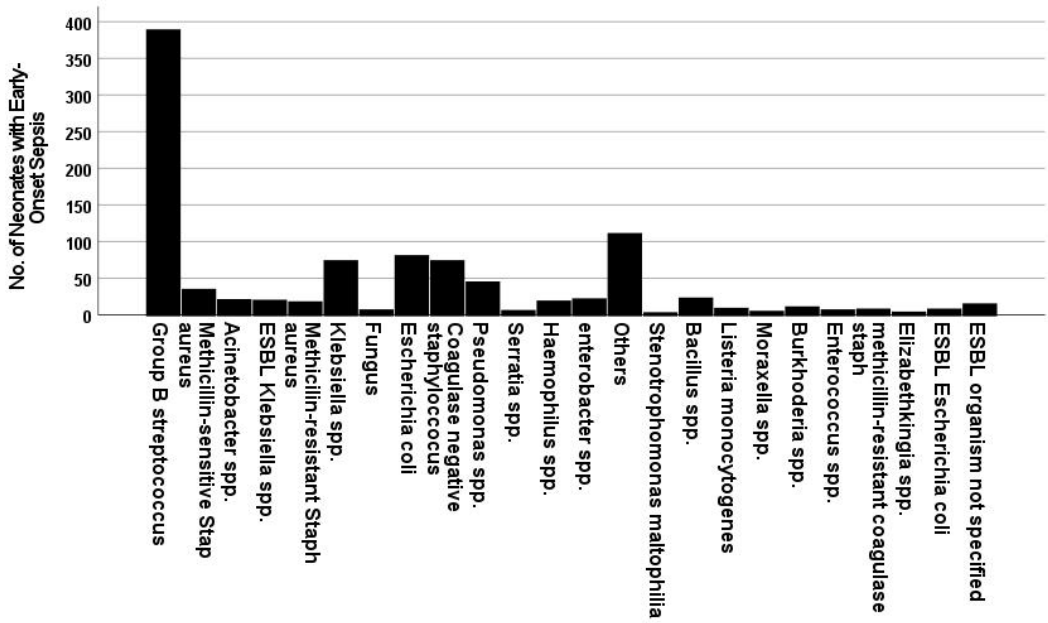


FIG. 1: Causative pathogens isolated in the blood of neonates of all birthweights and gestations with early-onset sepsis in the MNNR in years 2015-2010.
Notes: MSSA, methicillin sensitive *Staphylococcus aureus*; ESBL, extended spectrum Beta lactamase; MNNR, Malaysian National Neonatal Registry.

21.8%) was the most common, followed by CONS (n=19, 12.2%), *E. coli* (n=17, 10.9%), and Klebsiella spp. (n=16, 10.3%), In term (≥37 weeks gestation) neonates with EOS, GBS was most common (n=237, 56.4%), followed by *E. coli* (n=30, 7.1%), Klebsiella spp. (n=17, 4.0%) and CONS (n=17, 4.0%).

Of the 991 EOS neonates, 853 (86.1%) were

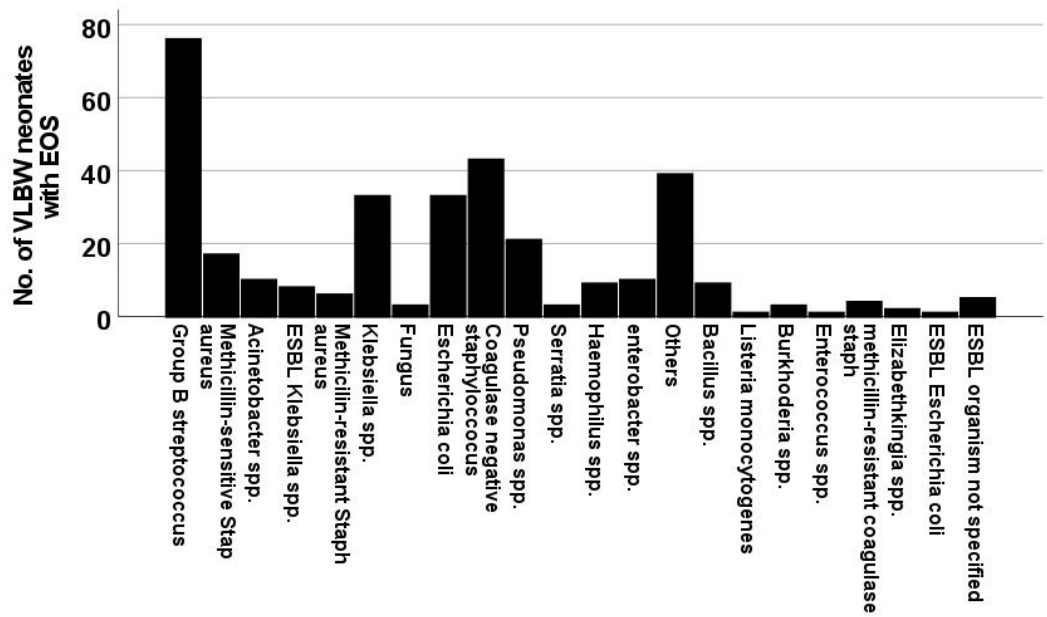


FIG. 2: Causative pathogens isolated in the blood of very low birthweight neonates with early-onset sepsis in the MNNR in years 2015-2010.
Notes: MSSA, methicillin sensitive *Staphylococcus aureus*; ESBL, extended spectrum Beta lactamase; MNNR, Malaysian National Neonatal Registry; VLBW, very low birthweight; EOS, early-onset sepsis.

inborn. The incidence of EOS was 0.48/1000 livebirths (range 0.40-0.57) with an increasing trend in 2018-2020 (Fig. 3). Of the 388 neonates with GBS EOS, 356 (91.8%) were inborn, giving an incidence of 0.20/1000 livebirths (range: 0.15-0.25) which increased gradually over the later three years. The incidence of EOS due to non-GBS pathogens was 0.28/1000 livebirths (range: 0.25-0.34); of these, E. coli EOS was 0.04/1000 livebirths (range: 0.02-0.05) and other pathogens was 0.24/1000 livebirths (range: 0.21-0.31).

There were 302/18766 (1.6%) inborn VLBW neonates with EOS, an incidence of 16.1/1000 VLBW livebirths. The five most common pathogens in inborn VLBW neonates were: GBS (n=70, 3.7/1000 VLBW livebirths), CONS (n=41, 2.2/1000 VLBS livebirths), *E.coli* (n=30, 1.6/1000 VLBW livebirths), Klebsiella (n=29, 1.5/1000 VLBW livebirths), and Pseudomonas spp. (n=16, 0.9/1000 VLBW livebirths).

Table 2 compares the neonatal and maternal characteristics between neonates with and without EOS. A significantly higher proportion of EOS neonates were VLBW, very preterm (VPT <32 weeks), appropriate for gestational age, female, singleton, and outborns than those without EOS. Mothers of EOS neonates were significantly younger, with lower gravid and parity status, and had significantly higher proportions of chorioamnionitis, antenatal steroids and intrapartum antibiotics. There were significantly higher proportions of EOS neonates with respiratory distress syndrome, LOS, patent ductus arteriosus, NEC, and meningitis; received mechanical ventilation (MV), high frequency ventilation (HFV), and inhaled nitric oxide therapy. A significantly lower proportion of them had received CPAP therapy in NICUs than those without EOS. They had significantly higher death rate, and longer duration of hospitalisation. The most common cause of death among the 273 EOS neonates was sepsis. The most common cause of death among 8671 neonates without EOS was major malformations.

*Neonates with GBS EOS, non-GBS EOS and without EOS*

Table 3 shows that mothers of GBS EOS neonates were significantly younger, with lower gravid and parity status; a higher proportion of them were Malays; they had more chorioamnionitis; a lower proportion of them had diabetes mellitus, antenatal steroids, and intrapartum antibiotics. There were significantly more GBS EOS neonates with birthweight ≥2500g, gestation ≥37 weeks, singletons, inborns, spontaneous vertex delivery and meningitis. There were significantly fewer GBS EOS neonates treated with eCPAP, bag-and-mask ventilation, endotracheal intubation, and surfactant therapy. They had lower death rate

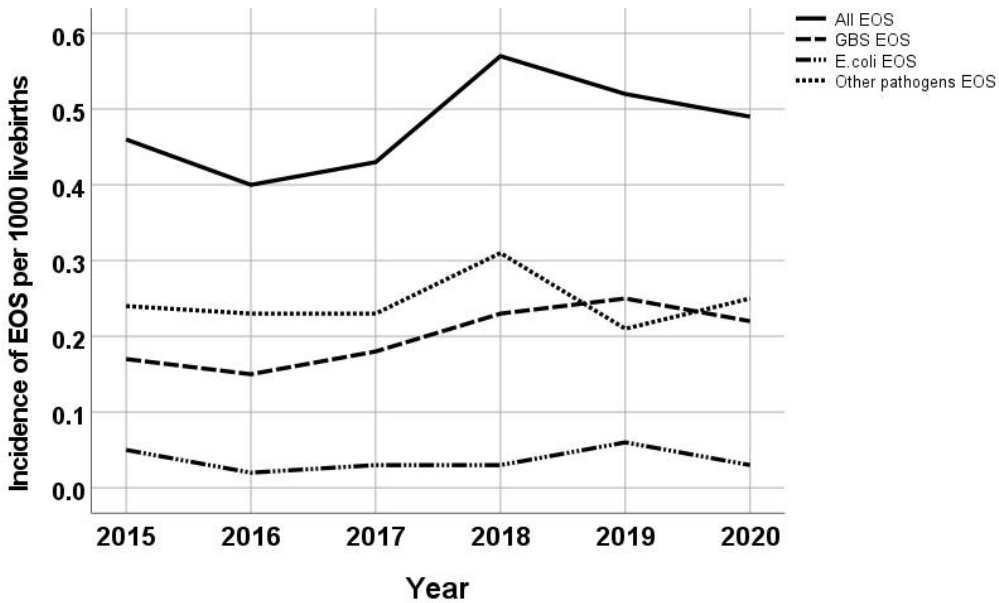


FIG. 3: Incidences of culture-positive early onset sepsis in inborn neonates in the Malaysian National Neonatal Registry from 2015 to 2020
Note: EOS, early-onset sepsis; GBS, group B haemolytic streptococci; *E.coli*, *Escherichia coli*.

**Table 2: Comparison of neonatal and maternal characteristics between neonates with and without early-onset sepsis in the Malaysian National Neonatal Registry, 2015-2020**

| Variables | Neonates with EOS N=991 (%) | Neonates without EOS N=96638 (%) | P values |
|---|---|---|---|
| **Maternal characteristics** | | | |
| | N=982 | N=95959 | |
| Age, mean±SD | 29.7 (5.7) | 30.1 (5.9) | 0.016 |
| | | N=96614 | |
| Gravida, median (range) | 2 (1-16) | 2 (1-19) | 0.044§§ |
| | N=982 | N=96597 | |
| Parity, median (range) | 1 (0-15) | 1 (0-15) | 0.014§§ |
| | | N=96616 | |
| No. of abortions, median (range) | 0 (0-6) | 0 (0-15) | 0.752 |
| Diabetes mellitus | 229/957 (23.9) | 25233/94416 (26.7) | 0.052 |
| Hypertension | 118/959 (12.3) | 11945/94581 (12.6) | 0.763 |
| Eclampsia | 32/964 (3.3) | 3555/95001 (3.7) | 0.491 |
| Anaemia | 184/957 (19.2) | 17970/94584 (19.0) | 0.858 |
| Abruptio placenta | 12/965 (1.2) | 1835 /95186 (1.9) | 0.123 |
| Bleeding placenta previa | 15/968 (1.5) | 3115/95197 (3.3) | 0.003 |
| Cord prolapse | 1/966 (0.1) | 344/95242 (0.4) | 0.274§ |
| Chorioamnionitis | 59/962 (6.1) | 2466/94962 (2.6) | <0.001 |
| Received antenatal steroid | 399/975 (40.9) | 35852/95231 (37.6) | 0.036 |
| Received intrapartum antibiotics | 206/968 (21.3) | 16573/95098 (17.4) | 0.002 |
| **Neonatal characteristics** | | | |
| Birthweight groups, g | | | |
| <1000 | 156 (15.7) | 5949 (6.2) | <0.001 |
| 1000-1499 | 181 (18.3) | 14351 (14.9) | |
| 1500-2499 | 250 (25.2) | 32250 (33.4) | |
| ≥2500 | 404 (40.8) | 44088 (45.6) | |
| Gestation, weeks | | | |
| <28 | 133 (13.4) | 4762 (4.9) | <0.001 |
| 28 to <32 | 202 (20.4) | 14472 (15.0) | |
| 32 to <37 | 236 (23.8) | 33750 (34.9) | |
| ≥37 | 420 (42.4) | 43654 (45.2) | |
| Intrauterine growth categories | | | |
| AGA | 736 (74.3) | 67525 (69.9) | 0.011 |
| SGA | 212 (21.4) | 24237 (25.1) | |
| LGA | 43 (4.3) | 4876 (5.0) | |
| Ethnic groups | | N=99609 | |
| Malay | 688 (69.4) | 65429 (67.7) | 0.313 |
| Chinese | 79 (7.9) | 7134 (7.4) | |
| Indian | 64 (6.5) | 5853 (6.1) | |
| Sabah native | 47 (4.7) | 5125 (5.3) | |
| Sarawak native | 35 (3.5) | 4367 (4.5) | |
| Orang Asli | 6 (0.6) | 1198 (1.2) | |
| Other Malaysian | 3 (0.3) | 531 (0.5) | |
| Foreigner | 69 (7.0) | 6972 (7.2) | |
| Gender | | | |
| Male | 535 (54.0) | 56778/96615 (58.8) | 0.010 |
| Female | 454 (45.8) | 39685/96615 (41.1) | |
| Indeterminate | 2 (0.2) | 152/96615 (0.2) | |
| Multiplicity | | | |
| Singleton | 943 (95.2) | 88943/96615 (92.1) | <0.001 |
| Multiples | 48 (4.8) | 7672/96615 (7.9) | |

| Variables | Neonates with EOS N=991 (%) | Neonates without EOS N=96638 (%) | P values |
|---|---|---|---|
| Admitted to NICUs | 991 (100) | 96475 (99.8) | 0.420§ |
| Place of birth | | | |
| Inborn | 853 (86.1) | 86771/96635 (89.8) | <0.001 |
| Outborn | 138 (13.9) | 9864/96635 (10.2) | |
| Major congenital malformations | 107 (10.8) | 10811 (11.2) | 0.698 |
| Respiratory distress syndrome | 444 (44.8) | 34994/96475 (36.3) | <0.001 |
| Meconium aspiration syndrome | 56 (5.7) | 9066 (9.4) | <0.001 |
| LOS | 82 (8.3) | 2641 (2.7) | <0.001 |
| PDA | 251/906 (27.7) | 12644/86905 (14.5) | <0.001 |
| NEC | 43 (4.3) | 1505/96475 (1.6) | <0.001 |
| Meningitis | 128 (12.9) | 1023/96475 (1.1) | <0.001 |
| CPAP therapy in NICU | 619 (62.5) | 69868/96475 (72.4) | <0.001 |
| Mechanical ventilation | 726 (73.3) | 54321/96475 (56.3) | <0.001 |
| High frequency ventilation | 257 (25.9) | 8290/96475 (8.6) | <0.001 |
| Inhaled NO therapy | 52 (5.2) | 1454/96475 (1.5) | <0.001 |
| Death | 273 (27.5) | 8671 (9.0) | <0.001 |
| Duration of hospitalisation, days Median (IQR) | | | |
| All neonates | 16 (7, 38) | 11 (5, 28) | <0.001 |
| Non-survivors | 3 (1, 9) | 2 (1, 10) | 0.049 |
| Survivors | 22 (12, 46) | 12 (6, 29) | <0.001 |
| Causes of death | N=273 | N=8671 | |
| Major malformations | 14 (5.1) | 2910 (33.6) | <0.001 |
| Sepsis | 140 (51.3) | 731 (8.4) | |
| Meningitis | 2 (0.7) | 19 (0.2) | |
| Other causes | 117 (42.9) | 5011 (57.8) | |

Note: § Exact test; §§ Mann-Whitney U test; SD, standard deviation; AGA, appropriate for gestation; SGA, small for gestation; LGA, large for gestation. EOS, early-onset sepsis; IQR, interquartile range; CPAP, continuous positive airway pressure; NICU, neonatal intensive care unit; NO, nitric oxide; LOS, late-onset sepsis; PDA, patent ductus arteriosus; NEC, necrotising enterocolitis.

and shorter duration of hospitalisation than non-GBS EOS neonates but had higher death rates and longer hospitalisation than those without EOS. Non-GBS EOS neonates had significantly lower birth weight and gestation, more outborns, received more bag-and-mask ventilation and endotracheal intubation in delivery room, more surfactant therapy, and needing more ventilation support than those with GBS EOS and without EOS. Significantly more neonates with GBS EOS had pneumonia and meningitis than neonates with non-GBS EOS and without EOS (p<0.001). Mortality rate was highest among non-GBS EOS neonates.

There were 2525 mothers with chorioamnionitis; 29 of them had neonates with GBS EOS, 30 had neonates with non-GBS EOS, and 2443 had neonates without EOS. Intrapartum antibiotics were given to 72.4% (21/29) of those with GBS EOS neonates, 56.7% (17/30) of those with non-GBS EOS neonates and 73.9% (1305/2443) of those with no-EOS neonates.

*EOS in VLBW neonates*

Of the 21136 VLBW neonates in the cohort, EOS status of 20637 (97.6%) neonates were known. Table 4 compares the characteristics and outcome of VLBW neonates with EOS due to GBS and non-GBS pathogens versus those without EOS. There was no significant difference in maternal demographic characteristics and use of antenatal steroids among the three groups. Compared with VLBW neonates without EOS, higher proportion of VLBW neonates with EOS due to GBS and non-GBS pathogens had chorioamnionitis, intrapartum antibiotics, extreme prematurity, vaginal delivery, surfactant therapy, pneumonia, and meningitis. They also had higher mortality rates, longer duration of hospitalisation, higher rates of death due to sepsis.

*Risk factors associated with GBS EOS*

Table 5 shows the results of multiple logistic regression analysis of potential risk factors

**Table 3: Comparison of maternal and neonatal characteristics between neonates with and without early-onset sepsis due to GBS and non-GBS pathogens**

| Variables | EOS due to GBS N= 388 | EOS due to Non-GBS Pathogens N= 603 | No EOS N= 96638 | P values |
|---|---|---|---|---|
| **Maternal characteristics** | | | | |
| Age in years, mean (±SD) | N=384<br>28.7 (5.4) | N=598<br>30.3 (5.8) | N=95959<br>30.1 (5.9) | <0.001 |
| Gravid status, median (IQR) | 2 (1, 3) | 2 (1, 4) | N=96614<br>2 (1, 3) | <0.001 |
| Parity | 1 (0, 2) | N=594<br>1 (0.2) | N=96597<br>1 (0, 2) | |
| Ethnic group | | | N=96609 | |
| Chinese | 21 (5.4) | 58 (9.6) | 7134 (7.4) | <0.001 |
| Malay | 299 (77.1) | 389 (64.5) | 65429 (67.7) | |
| Indian | 28 (7.2) | 36 (6.0) | 5853 (6.1) | |
| Other Malaysian | 17 (4.4) | 74 (12.3) | 11221 (11.6) | |
| Foreigner | 23 (5.9) | 46 (7.6) | 6972 (7.2) | |
| Diabetes mellitus | 80/379 (21.1) | 149/578 (25.8) | 25233/94416 (26.7) | 0.042 |
| Chorioamnionitis | 29/381 (7.6) | 30/581 (5.2) | 2466/94962 (2.6) | <0.001 |
| Antenatal steroids | 97/386 (25.1) | 302/589 (51.3) | 35852/95231 (37.6) | <0.001 |
| Intrapartum antibiotics | 66/386 (17.1) | 140/582 (24.1) | 16573/95098 (17.4) | <0.001 |
| **Neonatal characteristics** | | | | |
| Birthweight, g | | | N=96638 | |
| <1000 | 34 (8.8) | 122 (20.2) | 5949 (6.2) | <0.001 |
| 1000-1499 | 42 (10.8) | 139 (23.1) | 14351 (14.9) | |
| 1500-2499 | 86 (22.2) | 164 (27.2) | 32250 (33.4) | |
| ≥2500 | 226 (58.2) | 178 (29.5) | 44088 (45.6) | |
| Gestation, weeks | | | N=96638 | |
| <28 | 33 (8.5) | 100 (16.6) | 4762 (4.9) | <0.001 |
| 28 to <32 | 45 (11.6) | 157 (26.0) | 14472 (15.0) | |
| 32 to <37 | 73 (18.8) | 163 (27.0) | 33750 (34.9) | |
| ≥37 | 237 (61.1) | 183 (30.3) | 43654 (45.2) | |
| Intrauterine growth | | | | |
| AGA | 287 (74.0) | 449 (74.5) | 67525 (69.9) | 0.007 |
| SGA | 77 (19.8) | 135 (22.4) | 24237 (25.1) | |
| LGA | 24 (6.2) | 19 (3.2) | 4876 (5.0) | |
| Female | 192 (49.5) | 262 (43.4) | 39837/96615 (41.2) | 0.002 |
| Multiplicity | | | N=96615 | |
| Singleton | 383 (98.7) | 560 (92.9) | 88943 (92.1) | <0.001 |
| Multiples | 5 (1.3) | 43 (7.1) | 7672 (7.9) | |

| Variables | EOS due to GBS N= 388 | EOS due to Non-GBS Pathogens N= 603 | No EOS N= 96638 | P values |
|---|---|---|---|---|
| Place of birth | | | N=96635 | |
| Inborn | 356 (91.8) | 497 (82.4) | 86771 (89.8) | <0.001 |
| Outborn | 332 (8.2) | 106 (17.6) | 9864 (10.2) | |
| Mode of delivery | | | N=96599 | |
| SVD | 285 (73.5) | 293 (48.6) | 38668 (40.0) | <0.001 |
| Breech | 6 (1.5) | 20 (3.3) | 1247 (1.3) | |
| Forceps | 6 (1.5) | 4 (0.7) | 676 (0.7) | |
| Vacuum | 28 (7.2) | 21 (3.5) | 5781 (6.0) | |
| LSCS | 63 (16.2) | 265 (43.9) | 50227 (52.0) | |
| Early CPAP | 103/379 (27.2) | 240/591 (40.6) | 48503/94713 (51.2) | <0.001 |
| Bag-and-mask ventilation | 143/380 (37.6) | 284/589 (48.2) | 38727/94659 (40.9) | <0.001 |
| Endotracheal intubation | 144/380 (27.9) | 276/590 (46.8) | 35832/94692 (37.8) | <0.001 |
| Surfactant therapy | 107 (27.6) | 262 (43.4) | 22665/96475 (23.5) | <0.001 |
| Mechanical ventilation | 279 (71.9) | 447 (74.1) | 54321/96475 (56.3) | <0.001 |
| High frequency ventilation | 90 (23.2) | 167 (27.7) | 8290/96475 (8.6) | <0.001 |
| Pneumonia | 221 (57.0) | 193/589 (32.8) | 30704/96457 (31.8) | <0.001 |
| Meningitis | 65 (16.8) | 63 (10.4) | 1023/96475 (11.1) | <0.001 |
| Death | 83 (21.4) | 190 (31.5) | 8671/96638 (9.0) | <0.001 |
| Duration of hospitalisation Median (IQR) days | 14 (8,22) | 22 (7, 47) | 11 (5, 28) | <0.001 |
| Duration of hospitalisation of Survivors Median (IQR) days | N=305 15 (10, 25.5) | N=413 29 (16, 60) | N=87967 12 (6, 29) | <0.001 |
| Age of death, median (IQR)days | 2 (1,6) | 4 (2,11) | 2 (1, 10) | <0.001 |
| Causes of death | N=83 | N=190 | N=8671 | |
| Major malformations | 0 | 14 (7.4) | 2910 (33.6) | |
| Sepsis | 59 (71.0) | 81 (42.6) | 544 (6.3) | |
| Meningitis | 0 | 2 (1.1) | 19 (0.2) | |
| Other causes | 24 (28.9) | 93 (48.9) | 5198 (59.9) | |

Note: EOS, early-onset sepsis; GBS, group B haemolytic streptococci; CPAP, continuous positive airway pressure; IQR, interquartile range; SD, standard deviation; AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age; SVD, spontaneous vertex delivery; LSCS, lower segment Caesarean section.

**Table 4: Comparison of maternal and neonatal characteristics between VLBW neonates with and without early-onset sepsis due to GBS and non-GBS pathogens**

| Variables | EOS due to GBS N=76 | EOS due to Non-GBS Pathogens N=261 | No EOS N=20300 | P values |
|---|---|---|---|---|
| **Maternal characteristics** | | N=259 | N=20144 | |
| Age in years, mean (±SD) | 29.9 (5.9) | 30.5 (6.0) | 30.2 (6.2) | 0.354 |
| Gravid status, median (IQR) | 2 (1,3) | 2 (1,4) | N=20292<br>2 (1,3) | 0.585 |
| Parity | 1 (0,2) | N=258<br>1 (0,2) | N=20288<br>1 (0,2) | 0.524 |
| Ethnic group (%) | | N=261 | N=20290 | 0.131 |
| Chinese | 4 (5.3) | 27 (10.3) | 1811 (8.9) | |
| Malay | 59 (77.6) | 153 (58.6) | 13017 (64.2) | |
| Indian | 5 (6.6) | 18 (6.9) | 1290 (6.4) | |
| Other Malaysian | 3 (3.9) | 44 (16.9) | 2854 (14.1) | |
| Foreigner | 5 (6.6) | 19 (7.3) | 1318 (6.5) | |
| Diabetes mellitus (%) | 7/75 (9.3) | 52/246 (21.1) | 4753/19616 (24.2) | 0.006 |
| Chorioamnionitis (%) | 11/75 (14.7) | 19/249 (7.6) | 864/19792 (4.4) | <0.001 |
| Antenatal steroids (%) | 62 (81.6) | 200/254 (78.7) | 15434/19992 (77.2) | 0.561 |
| Intrapartum antibiotics (%) | 35/75 (46.7) | 79/251 (31.5) | 4695/19951 (23.5) | <0.001 |
| **Neonatal characteristics** | | | | |
| Birthweight, g (%) | | | | |
| <1000 | 34 (44.7) | 122 (46.7) | 5949 (29.3) | <0.001 |
| 1000-1499 | 42 (55.3) | 139 (53.3) | 14351 (70.7) | |
| Gestation, weeks (%) | | | | |
| <28 | 33 (43.4) | 100 (38.3) | 4714 (23.2) | <0.001 |
| 28 to <32 | 38 (50.0) | 132 (50.6) | 10238 (50.4) | |
| 32 to <37 | 5 (6.6) | 29 (11.1) | 5206 (25.6) | |
| ≥37 | 0 | 0 | 142 (0.7) | |
| Intrauterine growth (%) | | | | |
| AGA | 60 (78.9) | 206 (78.9) | 13608 (67.0) | <0.001 |
| SGA | 9 (11.8) | 51 (19.5) | 6279 (30.9) | |
| LGA | 7 (9.2) | 4 (1.5) | 413 (2.0) | |
| Female (%) | 39 (51.3) | 126 (48.3) | 9847/20289 (48.5) | 0.886 |
| Multiplicity (%) | | | N=20286 | |
| Singleton | 72 (94.7) | 231 (88.5) | 17042 (84.0) | 0.006 |
| Multiples | 4 (5.3) | 30 (11.5) | 3244 (16.0) | |
| Place of birth (%) | | | | |
| Inborn | 70 (92.1) | 232 (88.9) | 18464 (91.0) | 0.481 |
| Outborn | 6 (7.9) | 29 (11.1) | 1836 (9.0) | |

| Variables | EOS due to GBS N=76 | EOS due to Non-GBS Pathogens N=261 | No EOS N=20300 | P values |
|---|---|---|---|---|
| Mode of delivery | | | N=20287 | |
| SVD or Breech | 56 (73.7) | 127 (48.7) | 8239 (40.6) | <0.001 |
| Forceps or Vacuum | 0 | 1 (0.4) | 50 (0.2) | |
| LSCS | 20 (26.3) | 133 (51.0) | 11998 (59.1) | |
| Early CPAP (%) | 29 (38.2) | 129/259 (49.8) | 10570/19901 (53.1) | 0.019 |
| Bag-and-mask ventilation (%) | 56 (73.7) | 176/258 (68.2) | 10718/19892 (53.9) | <0.001 |
| Endotracheal intubation (%) | 57 (75.0) | 175/258 (67.8) | 10553/19896 (53.0) | <0.001 |
| Surfactant therapy (%) | 61 (80.3) | 200 (76.6) | 11943/20190 (59.2) | <0.001 |
| Mechanical ventilation (%) | 64 (84.2) | 216 (82.8) | 13196/20190 (65.4) | <0.001 |
| High frequency ventilation (%) | 26 (34.2) | 81 (31.0) | 3078/20190 (15.2) | <0.001 |
| Pneumonia (%) | 29 (38.2) | 69 (27.0) | 4366/20282 (21.5) | <0.001 |
| Meningitis (%) | 9 (11.8) | 23 (8.8) | 275/20190 (1.4) | <0.001 |
| Death (%) | 29 (38.2) | 104 (39.8) | 3853 (19.0) | <0.001 |
| Duration of hospitalisation Median (IQR) days | 42.5 (3.3, 78.3) | 42.0 (7.0, 70.0) | 42.5 (27.0 64.0) | 0.736 |
| Duration of hospitalisation of Survivors Median (IQR) days | 60..0 (44.0, 92.0) | 63.0 (44.0, 81.5) | 48.0 (35.0, 69.0) | <0.001 |
| Age of death, median (IQR)days | 2 (1, 6) | 5 (2, 11) | 2 (1, 10) | <0.001 |
| Causes of death (%) | | | | |
| Major malformations | 0 | 2 (1.9) | 654 (17.0) | |
| Sepsis | 15 (57.7) | 45 (48.9) | 336 (8.7) | |
| Meningitis | 0 | 0 | 0 | |
| Other causes | 14 (48.3) | 57 (54.8) | 2863 (74.3) | |

Note: EOS, early-set sepsis; GBS, group B haemolytic streptococci; CPAP, continuous positive airway pressure; IQR, interquartile range; SD,standard deviation; AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age; SVD, spontaneous vertex delivery; LSCS, lower segment Caesarean section;

associated with GBS EOS. There were 90415/97026 (93.2%) neonates with complete set of data for multiple regression analyses; of these 364 were GBS EOS neonates, and 90051 without EOS. After controlling for various potential confounders, seven factors were identified to be significantly associated with increased risk of GBS EOS. These were Indian ethnic group, chorioamnionitis, gestation≥37weeks, female, vaginal delivery, instrumental delivery, and surfactant therapy. Three factors were associated with significantly lower risk: other Malaysian ethnic group, outborns and eCPAP therapy. The p value for the Hosmer and Lemshow test of the multiple regression analysis was 0.989. The VIF of all independent variables were <4. The area under receiver operation characteristic (ROC) curve of the regression equation was: 0.793 (95% CI: 0.771, 0.816; p<0.001).

**Table 5: Multiple logistic regression analysis of potential risk factors associated with early-onset sepsis due to group B haemolytic streptococci in the Malaysian National Neonatal Registry of 2015-2020**

| Potential risk factors | Adjusted Odds Ratio (95% CI) | P values |
|---|---|---|
| Maternal age, mean±SD | 0.981 (0.959, 1.004) | 0.101 |
| Maternal parity | | |
| ≥3 | reference | |
| 1-2 | 1.117 (0.796, 1.568) | 0.522 |
| 0 | 1.369 (0.946, 1.981) | 0.095 |
| Ethnic groups | | |
| Chinese | reference | |
| Malay | 1.477 (0.924, 2.362) | 0.103 |
| Indian | 2.110 (1.172, 3.798) | 0.013 |
| Other Malaysians | 0.472 (0.241, 0.926) | 0.029 |
| Foreigners | 0.871 (0.445, 1.706) | 0.687 |
| Maternal diabetes mellitus | 0.872 (0.671, 1.134) | 0.307 |
| Chorioamnionitis | 4.119 (2.688, 6.311) | <0.001 |
| Antenatal steroids | 0.914 (0.641, 1.304) | 0.620 |
| Intrapartum antibiotics | 0.872 (0.640, 1.188) | 0.385 |
| Outborns | 0.464 (0.296, 0.727) | <0.001 |
| Birthweight, g | | |
| <1000 | reference | |
| 1000-1499 | 0.842 (0.443, 1.600) | 0.600 |
| 1500-2499 | 0.608 (0.282, 1.310) | 0.204 |
| ≥2500 | 0.625 (0.259, 1.511) | 0.297 |
| Gestation, week | | |
| <28 | reference | |
| 28 to <32 | 1.078 (0.562, 2.068) | 0.821 |
| 32 to <37 | 1.230 (0.551, 2.747) | 0.614 |
| ≥37 | 2.902 (1.157, 7.2779) | 0.023 |
| Growth status | | |
| AGA | reference | |
| SGA | 0.743 (0.546, 1.011) | 0.059 |
| LGA | 1.522 (0.984, 2.354) | 0.059 |
| Females | 1.461 (1.187, 1.799) | <0.001 |
| Mode of delivery | | |
| LSCS | reference | |
| SVD or breech | 5.131 (3.861, 6.818) | <0.001 |
| Instrumental delivery | 3.024 (1.922, 4.757) | <0.001 |
| Procedures received shortly after birth | | |
| Early CPAP therapy | 0.378 (0.298, 0.479) | <0.001 |
| Bag-and-mask ventilation | 0.807 (0.595, 1.095) | 0.169 |
| Had ETT intubation | 0.900 (0.657, 1.232) | 0.510 |
| Surfactant therapy | 2.270 (1.648, 3.128) | <0.001 |

Note: SD, standard deviation; AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age; LSCS, lower segment Caesarean section; SVD, spontaneous vertex delivery; CPAP, continuous positive airway pressure; ETT: endotracheal intubation; OR, odds ratio.

*Risk factors associated with non-GBS EOS*

Table 6 shows the results of multiple logistic regression analysis of potential risk factors associated with non-GBS EOS. There were 90582 neonates with complete set of data for analyses: 531 were neonates with non-GBS EOS, and 90051 without EOS. After controlling for various potential confounders, four factors were identified to be significantly associated with increased risk of non-GBS EOS: outborns, extremely low birthweight (ELBW, <1000g), vaginal delivery, and surfactant therapy. eCPAP was identified to be significantly associated with lower risk. The VIF of all independent variables were <4; the Hosmer and Lemshow test p=0.095. The area under ROC curve was 0.696 (95% CI: 0.674, 0.719; p<0.00).

## DISCUSSION

In this 6-year study of neonates admitted to 62.8 % (44/70) of NICUs in Malaysia, the annual incidence of culture-positive EOS showed an increasing trend in the later three years. This increase was mainly due to an increased incidence of GBS, the most common causative pathogen affecting all birthweights and gestational age. Most of the GBS EOS neonates were term/normal birthweight neonates; most of the non-GBS EOS neonates were preterm and/or low birthweight neonates. Compared with neonates without EOS, the duration of hospitalisation, morbidities and mortalities were significantly higher in those with EOS, and mortality was highest among those with non-GBS EOS.

Although the EOS incidence (0.48/1000 livebirths) in our cohort was lower than those reported in HICs (≥ 0.7/1000 livebirths),[5,6,11,12] these population-based studies in HICs were done before 2015 while our findings were based on data of 2015-2020. Recent studies reported from HICs were mainly on VLBW/very preterm neonates. In USA, the incidence of EOS among VLBW was 1.08 (95% CI: 0.95-1.23) cases per 1000 livebirths between 2015-2017,[13] and in Australia and New Zealand it was 0.14/1000 livebirths.[14] In the present study, the incidence of EOS among VLBW neonates in Malaysian NICUs (at 16.1/1000 live births) was very much higher.

Like NICUs of many HICs,[5-7] GBS was the most frequent pathogen isolated in EOS in Malaysia. The incidence of *E. coli* remained very low in neonates of all birthweight and gestation during this period in Malaysia. In recent years, E. *coli* was the most common EOS pathogen affecting VLBW/preterm neonates with a rising trend in USA,[13] Canada,[15] Germany,[8] and Australia and New Zealand.[14] One possible explanation for these differences between NICUs in HICs and Malaysia could be the different national strategies used to prevent GBS. Currently, all pregnant mothers can be screened antenatally at 35-37 weeks for GBS colonisation (universal screening) or selectively during intrapartum period when presented with fever, or prolonged rupture of amniotic membrane or premature labour (risk-based screening). When GBS is detected by either approach, intrapartum prophylactic antibiotics (IPA) is then administered. Although IPA alone in high risk mothers has resulted in life-saving effects of neonates of maternal GBS colonisation,[16] population studies in HICs showed that universal antenatal screening for maternal GBS colonisation between 35-37 weeks gestation further resulted in significantly lower incidence of GBS EOS than risk-based screening.[17] Since 2002, the Centre for Disease Control and Prevention in USA has recommended universal screening of all pregnant women for rectovaginal GBS colonisation at 35-37 weeks' gestation and administration of IPA to carriers.[18] In Malaysia, we do not have a national policy for universal antenatal screening. We have a national guideline for IPA for "mother with previous baby with invasive GBS disease, preterm labour, GBS carriage in previous pregnancy, prolonged premature rupture of membrane in known GBS carrier, GBS carriage in current pregnancy, and for maternal chorioamnionitis".[19]

Our study concurred with findings elsewhere that chorioamnionitis was a significant risk factor associated with EOS,[20] and that delivery via vaginal route was a significant factor associated with increased risk.[7] Vaginal delivery is a critical point in the transfer of microbes between mother and child,[21] particularly in the presence of chorioamnionitis, leading to bloodstream invasion of mucosa of neonates and resultant EOS. We found that <75% of maternal chorioamnionitis in our cohort received IPA. This could be an important reason accounting for IPA not being identified as a significant factor associated with lower risk of EOS in our cohort unlike those reported by others.[16] Like findings elsewhere, we found antenatal steroids was not a significant risk factor.[22]

The present study did not show any association of decreasing gestational age with an increased risk of EOS.[2,13] Instead, term gestation was a

**Table 6: Multiple logistic regression analysis of potential risk factors associated with early-onset sepsis due to non-group B haemolytic streptococcal pathogens in the Malaysian National Neonatal Registry, 2015-2020**

| Potential risk factors | Adjusted OR (95% CI) | P values |
|---|---|---|
| Maternal age, mean±SD | 1.010 (0.993, 1.028) | 0.250 |
| Maternal parity | | |
| 0 | Reference | |
| 1-2 | 0.923 (0.754, 1.130) | 0.439 |
| ≥3 | 1.014 (0.772, 1.333) | 0.918 |
| Ethnic groups | | |
| Chinese | Reference | |
| Malay | 0.887 (0.655, 1.201) | 0.440 |
| Indian | 0.915 (0.584, 1.434) | 0.699 |
| Other Malaysians | 0.911 (0.623, 1.331) | 0.629 |
| Foreigners | 0.878 (0.559, 1.378) | 0.571 |
| Maternal diabetes mellitus | 1.038 (0.848, 1.271) | 0.718 |
| Chorioamnionitis | 1.451 (0.972, 2.164) | 0.068 |
| Antenatal steroids | 1.224 (0.956, 1.568) | 0.109 |
| Intrapartum antibiotics | 1.231 (0.991, 1.529) | 0.061 |
| Outborns | 1.837 (1.410, 2.393) | <0.001 |
| Birthweight, g | | |
| ≥2500 | Reference | |
| 1500-2499 | 1.076 (0.748, 1.549) | 0.692 |
| 1000-1499 | 1.529 (0.943, 2.481) | 0.085 |
| <1000 | 2.333 (1.288, 4.223) | 0.005 |
| Gestation, week | | |
| ≥37 | Reference | |
| 32 to <37 | 0.902 (0.625, 1.301) | 0.581 |
| 28 to <32 | 1.156 (0.698, 1.914) | 0.574 |
| <28 | 1.431 (0.763, 2.685) | 0.264 |
| Growth status | | |
| AGA | Reference | |
| SGA | 0.901 (0.700, 1.159) | 0.416 |
| LGA | 0.761 (0.473, 1.222) | 0.258 |
| Females | 1.068 (0.897, 1.270) | 0.460 |
| Mode of delivery | | |
| LSCS | reference | |
| SVD or breech | 1.397 (1.156, 1.689) | <0.001 |
| Instrumental delivery | 1.096 (0.683, 1.757) | 0.705 |
| Procedures in DR | | |
| Early CPAP therapy | 0.688 (0.573, 0.825) | <0.001 |
| Bag-and-mask ventilation | 1.110 (0.878, 1.401) | 0.383 |
| Had ETT intubation | 0.908 (0.709, 1.163) | 0.444 |
| Surfactant therapy | 1.506 (1.188, 1.910) | <0.001 |

Note: SD, standard deviation; AGA, appropriate for gestational age; SGA, small for gestational age; LGA, large for gestational age; LSCS, lower segment Caesarean section; SVD, spontaneous vertex delivery; CPAP, continuous positive airway pressure; ETT: endotracheal intubation; OR, odds ratio.

significant risk factor associated with GBS and ELBW a risk factor associated with non-GBS EOS. Furthermore, neonates of Indian ethnic group were associated with significantly higher risk while 'other Malaysians' were associated with lower risk of GBS. Genetic predisposition and different cultural practices could be the underlying mechanisms. No previous studies have identified female neonates as a risk factor associated with EOS as in this study. We are not able to explain the underlying mechanism of this risk factor.

Outborns was identified as a significant risk factor associated with increased risk of EOS due to non-GBS pathogen but not GBS, suggesting extrauterine acquisition of non-GBS infection during transport could be a possible mechanism. To the best of our knowledge, no previous studies have reported on the role of surfactant therapy and eCPAP as risk factors associated with EOS. In the present study, there were more neonates with EOS receiving resuscitation and surfactant therapy at birth than those without EOS. However, after controlling for various potential confounders, only surfactant therapy was associated with significantly increased risk and eCPAP was associated with lower risk. Compared with either bag-and-mask ventilation and/or endotracheal tube intubation, the process of instillation of surfactant therapy promotes deeper and wider dispersion of pathogens into the lungs either from a contaminated endotracheal tube or surfactant solution, or from the oral-pharyngeal area of a neonate who has inhaled/ingested pathogen during birth. eCPAP therapy is a much less invasive respiratory support and was thus associated with significantly lower risk of EOS. Based on these findings, to reduce EOS in Malaysian NICUs, improving training and monitoring of health care providers in proper sterile techniques of instillation of surfactant in neonates should be considered; and eCPAP therapy should be promoted as a first line respiratory support in neonates who need it.

GBS infection is not uncommon in Malaysia and has been reported even among non-pregnant adults.[23] Given the increasing incidence of GBS EOS in Malaysian NICUs and its associated high morbidities and mortality, and the low use of IPA for chorioamnionitis, several preventive strategies should be considered. These include universal antenatal screening for GBS at 35-37-week gestation, close monitoring of compliance of use of IPA for high-risk pregnancies, provision of adequate facilities and active promotion of eCPAP in neonates with respiratory distress in delivery rooms, and systematic training and monitoring of all front-line healthcare providers on adherence to strict sterility during surfactant instillation in neonates.

This study has several strengths: a) it was the first national study on epidemiology of EOS in a middle-income country; b) it has a large sample size; c) the data were prospectively collected using a standardised format; d) 62.8% of the NICUs in Malaysia participated in this study and they delivered 68% of all livebirths and 93% of all low birthweight (<2500g) neonates in Malaysia,[24] and e) neonates of all gestation and birthweight with EOS were evaluated.

The major limitation of this study is our inability to determine whether a history of prolonged rupture of membrane or premature rupture of membrane were significant risk factors associated with EOS as these data were not captured in the MNNR database.

In summary, the incidence of EOS showed an increasing trend in Malaysian NICUs. GBS was the most common pathogen. Incidence in VLBW neonates were higher than those in HICs. Several modifiable risk factors associated with EOS have been identified.

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**What is already known?**

- E. coli has overtaken group B haemolytic streptococci as the most common causative pathogen of neonatal early-onset sepsis in many neonatal intensive care units in high-income countries in recent years.
- Neonatal early-onset sepsis is associated with high morbidities and mortality.
- Chorioamnionitis is a significant risk factor associated with neonatal early-onset sepsis.

**What this study adds:**

- Group B haemolytic streptococci remains the most common causative pathogen of neonatal early onset-sepsis in all gestational and birthweight groups in the neonatal intensive care units of a middle-income country.
- Surfactant therapy is a significant factor associated with increased risk of neonatal early-onset sepsis.
- Use of early continuous positive airway pressure therapy is associated with significantly lower risk of neonatal early-onset sepsis.

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