**Association between early onset culture-proven neonatal sepsis and maternal genital colonisation - A retrospective cross-sectional study**

**Abstract:**

In the present study, we analysed the clinical profile and maternal genital colonisation patterns in 74 neonates with culture proven early onset neonatal sepsis (EOS) over 18 months. Maternal vaginal colonisation was identified in 65% cases with EOS, with E.coli being the commonest pathogen. Concordant growth in neonates and mothers were found in 18.33% cases. Case fatality rate was 55.4%.

**Introduction**

Sepsis and its related complications are leading causes of neonatal mortality and morbidity responsible for a quarter of neonatal deaths globally (1,2,3).  In 2013, 38.9% of neonatal sepsis related deaths occurred in South Asia where neonates with culture positive sepsis had a high median case fatality rate of 34.4% (4). The distinction between early onset (0-72 hours) and late onset (after 72 hours) infections are mainly based on the probable risk factors and aetiology, with early onset acquired from the mother in-utero or intrapartum,(3,5) while late onset is acquired through horizontal transmission from the hospital environment. (4), but there has been an increasingly high number of EOS, which has been attributed to ultra-short horizontal transmission as well (1,3,6), while certain infections like group B streptococcal (GBS) infection can present late, though they are acquired during labour. The present study intended to analyse the proportion of deliveries where culture proven EOS was associated with maternal vaginal colonisation.

**Methods:**

This retrospective cross-sectional study was conducted in the JIPMER NICU, between July 2022 and December 2023. Neonates with culture-proven EOS were selected from case records and the following data were collected: gestational age, birth weight, gender, and relevant maternal risk factors (e.g., PROM, preterm labour, unclean PV examinations, and chorioamnionitis). Data on maternal comorbidities, mode of delivery and maternal swab culture results was also included. Neonatal outcomes such as APGAR scores, need for resuscitation, mode of respiratory support, symptomatology, duration of NICU stay, mortality and antibiotic sensitivity. Blood cultures were done using matrix-assisted laser desorption/ionization – time of flight mass spectrometry (MALDI-TOF MS), and antimicrobial susceptibility done by VITEK. The sample size was determined based on past data, with an anticipated 15% prevalence of maternal genital tract colonization in neonates with early onset sepsis, leading to a required sample size of 204. However, considering the incidence of EOS in the unit, we decided to look at data from 80 neonates collected over the past two years. The primary objective was to estimate the proportion of neonates with culture positive early onset neonatal sepsis that were associated with maternal genital colonisation. Secondary outcomes included mortality and morbidity profiles of neonates with culture proven EOS. Approval of the institute ethics committee was obtained prior to study commencement (JIP/IEC-OS/2024/61). STATA version 17.0 software was used to analyze data.

**Results:**

During the 18-month study period, there were 18120 livebirths and 3308 NICU admissions (Fig 1). Out of these, 79 neonates were diagnosed with culture-positive EOS, amounting to an incidence of 4.4 EOS per 1000 livebirths or 2.4 EOS cases per 100 NICU admissions. After excluding 5 neonates (due to missing data), 74 were enrolled for the study. Baseline characteristics and outcomes are tabulated in table 1.

The commonest pathogens implicated in the blood culture of neonates with EOS were: Klebsiella pneumoniae (n=22), E.coli (n=13), Acinetobacter baumannii (n=13) and Pseudomonas aeruginosa (n=13). Maternal swab reports were available for 81.1% of the EOS cases (60/74), out of which 65% had some colonization (39/60), with the commonest pathogens being E.coli (n=26), Klebsiella pneumoniae (n=4) and GBS (n=3). Concordant growth in maternal genital tract and neonatal blood culture samples were seen in 18.33% cases (11/60), with the concurrence being highest for E.coli (8 out of 16 neonates with E.coli sepsis had maternal genital colonisation with the same organism). The mortality rate was 55.4%. The survivors (n=33) had an average hospital stay of 36 days. 55.4% (n=41/74) of the causative organisms were multi drug resistant. Neutropenia (<1800 Neutrophils/mm3) and leukopenia (<5000 Leukocytes/mm3) were observed in 40 (53.3%) neonates. None of the identified covariates were significantly associated with mortality in univariable analysis.

**Discussion:**

**Maternal Genital Tract Colonisation**

The present study was conducted to study the maternal genital colonisation patterns in neonates with culture proven EOS. We found that colonisation was prevalent in 65% of mothers, whose neonates developed culture proven EOS, while concordant growth in maternal genital tract and neonatal blood culture was seen in 18.33% cases. A previous systematic review analysing colonisation patterns in mothers found out that only 1.3% of neonates born to mothers with genital colonisation developed culture proven sepsis (22 studies; 125 neonatal infections out of 9399 mothers who had colonisation). Almost all (20 studies, 1 each on MRSA and Klebsiella) of the studies were on GBS and the authors pointed out in their results that there is lack of data from LMICs, where neonatal mortality due to EOS is higher, and organisms other than GBS predominate (2). Elliyas et al observed that the prevalence of bacterial colonisation in low-risk mothers with intact membranes was 52.6% (19). Okomo et al (27) noted from West Africa noted in their study that all 36 mothers whose neonates had culture-proven EOS had evidence of genital bacterial colonisation (100%), though only 13.8% (5/36) had concordant organisms in maternal genital tract and neonatal blood culture. Another study conducted (10) looking at maternal genital tract colonization with selected potential pathogens of neonatal sepsis showed that 18.8% had Enterobacteriaceae colonisation. They also suggest that maternal genital tract colonisation might be an important risk factor for early onset neonatal sepsis. In a study conducted in Pakistan in 2008, the *E. coli* colonization among pre-delivery mothers has been reported as 13.7% (*n* = 100), while the colonization rate for *Klebsiella pneumoniae* was 10.5% (*n* = 77). (11) Another study conducted in Argentina in 2012 revealed 18.55% (*n* = 48) colonization rate for Enterobacteriaceae among 259 pregnant women, and the species-specific colonization rates were 14.3% (*n* = 37) for *E. coli* and 1.2% (n = 3) *Klebsiella pneumoniae***.**

We observed that the incidence of maternal genital tract colonisation is significantly higher, 65% of which in mother’s whose children have been diagnosed with EOS. This could be explained by the fact that we included only culture proven EOS cases, where the likelihood of maternal genital colonisation is higher. Further analysis showed that out of these 39 women, 87.2% (n=34) had Enterobacteriaceae colonisation. This accounts for 55.7% for whom a vaginal swab was performed. This is significantly higher than the previously reported 18.55% in Argentina or 18.8% in Sri Lanka.

The low concordance rates amongst other gram negative pathogens and predominance of nosocomial organisms in blood cultures can be attributed to ultra short horizontal transmission from the hospital environment as suggested by previous studies. (1,20,21)

**Causative Organisms**

Most of the infection load in our study was caused by 4 causative organisms, *E. coli, P. aeruginosa, K. pneumoniae* and *A. baumanii*. These four organisms together caused 81.08 % (n=60) of the EONS cases. Fungal sepsis was also observed with an incidence of 4.04% (n=3) with both *Candida albicans* and *Candida tropicalis* causing these infections. Previous studies identified Group B Streptococcus (GBS) as a major causative organism for EOS, responsible for 38-43% of all EOS cases in the US (12). The most frequent pathogens as per this study were Escherichia coli (86 [36.6%]) and group B streptococcus (GBS; 71 [30.2%]). Another study (13), showed that GBS (38%) and E coli (24%) were the major causative organisms. In 2011, a study (14) conducted in the US showed that the incidence of GBS and E Coli EOS was 43% and 29% respectively. Previously mentioned studies were mainly conducted in high income countries with a predisposition to GBS sepsis. On the contrary, we found that only 4.04% had GBS (n=3) infection. The three studies mentioned above see an incidence of 24-36.6% of E Coli sepsis. Our study had a slightly lower incidence with 17.56% (n=13) of all EOS caused by the organism. A study conducted in Serbia (7) between 2013 and 2015 revealed that *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Escherichia coli*, *Serratia*, and *Citrobacter* were most frequently identified in EOS which correlates with the findings of our study.

**Antibiotic Prophylaxis and Multi Drug Resistance**

The incidence of MDR pathogens was 55.4% (41/74) which was almost identical to the previously reported 55.37% from China in 2023. (22) In Singapore, MDR isolates were seen in 47% of the neonatal sepsis infections.(24). Mortality rate was similar between MDR sepsis and non MDR sepsis, 56.09% and 54.54% respectively. A study from Jordan reported that sepsis due to MDROs was associated with a significantly higher mortality rate as compared to non-MDRO sepsis (60% *vs*. 13%) (23). However, the DeNIS study, conducted in Delhi reported that the population attributable risk of mortality was 15.7% in culture-positive sepsis by MDRO *vs*. 12.0% in culture-positive sepsis by non-MDRO. (1)

Acinetoacter Baumanii (n=10), Klebsiella Pneumoniae (n=16), Escherichia Coli (n=7) were the major MDR organisms (n=33/41, 80.48%). As per a recent study from Delhi (1), of 1005 culture positive cases, the commonest organisms isolated were *Acinetobacter baumannii* (22%) followed by *Klebsiella pneumoniae* (17%) and *Escherichia coli* (14%). There were high rates of multidrug resistance (resistance to any three of five antibiotic classes) in *Acinetobacter baumannii* (82%), *Klebsiella pneumoniae* (54%), and *Escherichia coli* (38%) isolates. In a separate cohort study conducted in Delhi, the multi-drug resistance rates for Klebsiella pneumoniae, A. baumannii, E. coli, and E. cloacae were found to be 65.4%, 71.4%, 78.7%, and 66.0%, respectively. (25)

In our study high rates of MDR was obsered in *Acinetobacter baumannii* (76.9%), *Klebsiella pneumoniae* (72.72%), and *Escherichia coli* (53.84%) isolates.

32/74 received antibiotics for risk factors and showed greater mortality rates in comparison to those who didn’t. 22/32 (68.7%) as compared to 19/42 (45.3%). 33/74 mother’s were also treated with antibiotics antepartum and 21/33 (63.6%) of their children succumbed to EONS. while amongst the 41 mothers who did not receive antibiotics. mortality rates were lower amongst their children at 48.7% (20/41)

**Risk Factors**

A meta-analysis was conducted in China (15) where a total of 17 studies were included on major perinatal risk factors for EOS. It was revealed that perinatal asphyxia, amniotic fluid meconium contamination, GBS colonisation in pregnant women, chorioamnionitis, PROM, lower gestational age, perinatal fever, VLBW, >3 P/V examinations and maternal UTI/reproductive tract infection were major risk factors for EOS (16). Common maternal risk factors for EOS included PROM (17), chorioamnionitis, and maternal comorbidities such as gestational diabetes and hypertension. Over 50% of the neonates requiring respiratory support were born to mothers with these risk factors.

**Mortality Rate**

One of the objectives of this study was to find the mortality rate amongst Neonates with EOS. The overall mortality rate in this study was 56%, which is significantly higher than previously reported rates of 37.5% in similar studies (7). It was closer to the postulated 54% as per an article published in 2017 (18). A study conducted in the United States between 2005 and 2008 reported the mortality rate to be closer to 10.9% with *E. coli* (24%) and GBS (38%) being the major causative organisms. (13) This high mortality rate suggests the severity of EOS in the study population, with Gram-negative organisms being particularly fatal. The mortality rate was similar among neonates born to colonized and non-colonized mothers, indicating that factors other than maternal colonization alone may contribute to poor outcomes.

**Advantages**

To the best of the authors’ knowledge, this is one of the few studies to look at maternal genital tract colonisation patterns in mothers of neonates with early onset sepsis. Despite the small sample size, this study provides a holistic outlook into EOS, its epidemiology, risk factors, clinical outcome and causative organisms. The use of blood cultures to confirm suspected EONS, MALDI-TOF for pathogen identification and VITEK for antimicrobial susceptibility testing further strengthens the study. Maternal genital colonization as a significant risk factor to neonatal sepsis, might be relevant in *E. coli* infections, while the same may not be true for other culture proven EOS cases.

**Limitations**

The major limitation of this study is its sample size of 74. Though consequential, the size was smaller than initially required. This might have limited the statistical power, resulting in the under-representation or misrepresentation of some trends. Similarly, swab results were available for 61 mothers, which could decrease the robustness of the conclusions regarding maternal colonization. The study was a single centre study, limiting the generalizability of the findings to other regions or healthcare settings.

Further research on incidence of concordant infections and MDR pathogen sepsis in LMIC will prove to be beneficial. The high incidence of maternal genital tract colonisation and neonatal mortality in this study warrants more studies to be conducted in this domain, with a larger sample size in similar low resource settings.

**Conclusion**

This retrospective study looked at 74 neonates diagnosed with culture-proven early-onset neonatal sepsis (EOS) admitted to a tertiary healthcare centre in South India. The study looked into the role of maternal genital tract colonization and its association with EOS, and found that 65% (n=39/60) had maternal genital colonization. The most commonly isolated organism from the maternal genital tract was Escherichia coli (n=26). It caused 17.56% of all EOS cases, aligning with global trends. (12-14). 18.33% of neonates (n=11) showed concordant infections where the same organism was found in both maternal and neonatal cultures. This observation reinforced the link between maternal colonization and neonatal sepsis. The study shows that maternal colonization, especially with *E. Coli*, plays a significant role in the pathogenesis of EOS.

The mortality rate was 56%, higher than the previously reported rates of around 37.5%. (7). Gram-negative bacteria (*Klebsiella pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa, Escherichia Coli*) caused most of these infections. However, Streptococcus agalactiae (Group B Streptococcus), a common cause of EOS in Western countries, contributed to only a minority of the cases (4.04%). (12-14) 55.4% of the pathogens were multi drug resistant showcasing the high rates of MDR EONS in LMIC countries as suggested by previous studies. (26)

**Table 1: Baseline characteristics and outcomes of neonates with culture proven EOS**

| Parameter | Number (N=74) | 95% CI / Range |
| --- | --- | --- |
| Mean GA in wk (SD) | 32.8 (4.8) | 24-43 |
| Median birthweight in g | 1330 | 600-3880 |
| Males | 39 (52.7%) | 40.2-63.7 |
| Vaginal delivery | 34 (46.0%) | 33.8-57.3 |
| Maternal comorbidities | 51 (68.9%) | 56.2-78.3 |
| Receipt of antibiotics for risk factors for sepsis | 32 (43.2%) | 31.3-54.6 |
| Perinatal asphyxia (1 min APGAR <4) | 22 (29.7%) | 19.4-40.1 |
| Need for resuscitation | 32 (43.2%) | 31.3-54.6 |
| Delivery room CPAP | 39 (52.7%) | 40.2-63.7 |
| PROM | 39 (52.7%) | 40.2-63.7 |
| Prolonged ROM | 15 (20.3%) | 11.8-31.2 |
| MSL | 23 (31.1%) | 20.8-42.9 |
| Clinical chorioamnionitis | 7 (9.5%) | 3.5-18.5 |
| Spontaneous onset preterm labour without PROM | 9 (12.2%) | 5.7-21.8 |
| Maternal fever | 10 (13.5%) | 6.6-23.2 |
| >3 PV examinations | 38 (51.4%) | 39.4-63.1 |
| Steroid coverage in preterm (N=51)   * Any dose * Full course | 40 (78.4%)  20 (39.2%) | 64.7-88.7  25.8-53.9 |
| Intrapartum antibiotics | 33 (44.6%) | 33.0-56.6 |
| Growth in maternal high vaginal swab | 60 (61.6%) | 51.6-76.9 |
| Concordant growth in maternal vaginal swab and neonatal blood culture | 13 (21.7%) | 12.1-34.2 |
| Mean age of symptom onset in hours (SD)  Median | 27 (15)  23 | 6-70 |
| Symptomatology   * Respiratory distress * Shock * Apnea * Bleeding | 54 (72%)  54 (72%)  25 (33.3%)  49 (65.3%) | 60.4-81.8  60.4-81.8  22.9-45.2  53.5-76.0 |
| Highest mode of respiratory support   * None * CPAP/ HFNC * NIV   Invasive ventilation | 6 (8%)  11 (14.7%)  8 (10.7%)  50 (66.7%) | 21.7-43.8  7.6-24.7  4.7-19.9  54.8-77.1 |
| Total duration of respiratory support (median) | 3 | 1-72 |
| Meningitis | 15 (20.3%) | 11.6-30.8 |
| Hydrocephalus | 1 (1.3%) | 0.03-7.2 |
| Ventriculitis | 1 (1.3%) | 0.03-7.2 |
| AKI | 7 (9.5%) | 3.5-18.5 |
| Shock | 51 (68%) | 56.2-78.3 |
| Mortality | 41 (55.4%) | 43.4-67.0 |
| MDR | 41 (55.4%) | 43.4-67.0 |

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