Optimizing use of empirical antibiotics in late preterm neonates at risk of early-onset sepsis

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ABSTRACT

Background: In sick neonates, we are posed to treat suspected or proven infection. However, the vast majority of newborn babies who are given antibiotics do not have any infection. **Objective:** The objective of this study was to optimize the use of empirical antibiotic therapy in late preterms who are asymptomatic with maternal risk and symptomatic neonates without maternal risk for early-onset sepsis (EOS) and to estimate the rate of risk increase in onset of symptoms in neonates exposed to maternal risk factor for EOS. **Methods:** In this descriptive study, late preterm neonates (34^{+0}–36^{+6} weeks) who are asymptomatic at birth with and without maternal risk factor for EOS at birth were subjected to clinical assessment of sensorium, temperature, oxygenation status, perfusion, and skin color, starting after 1 h of initial stabilization till discharge from hospital. Sepsis screen (C-reactive protein and absolute neutrophil count) was obtained at 24 h and 48 h of age from these asymptomatic late preterms. **Results:** A total of 135 late preterm neonates (34^{+0}–36^{+6} weeks) recruited during the study period were included for analysis. The presence of maternal risk factor for EOS has shown no statistical significance in relation to the presence of symptoms at birth odds ratio 0.66, 95% confident interval (0.24–1.8) p=0.42. **Conclusion:** In our study, as maternal risk factor for sepsis has shown no statistical significance in relation to the presence of symptoms at birth, antibiotic use can be restricted to only those babies who have clinical worsening over 24–48 h of observation and/or along with supportive evidence of positive sepsis screen and/or blood culture, irrespective of the presence or absence of maternal risk for EOS.

Key words: Early-onset sepsis, Late preterm, Neonates, Risk factors

Widespread and overuse of antibiotics are associated with antibiotic resistance and loss of microbiota. Furthermore, studies have shown that prolonged duration of empiric antibiotic therapy for early-onset sepsis (EOS) has been associated with increased risk of death and necrotizing enterocolitis. In addition, overuse of antibiotics can cause adverse events such as nephrotoxicity, hepatotoxicity, and hematological abnormalities. For these reasons, asymptomatic neonates at birth with risk factor for EOS should have minimal exposure to antibiotics [1].

Identification of early neonatal sepsis is a major issue due to limitations in diagnostic procedures and severity of the outcome. The gold standard of positive blood culture has very low sensitivity [1]. The incidence of preterm births (<37 weeks gestation) is increasing in many countries around the world and has become a global health concern. More than 70% of preterm infants are born between 34 and 36 weeks of gestation [2]. Minimizing antibiotic exposure among these groups of infants without risk is not an easy task. Different screening tests and combination of tests including acute-phase reactants, hematological scoring systems, and recently cytokines are used for the identification of

early-onset neonatal sepsis (EONS) and the optimal selection of which is yet to be determined; cost can also be limiting. Good negative predictive values can be obtained at 12–24 h of life (99%) with C-reactive protein (CRP) [3-5].

Infants hospitalized in neonatal intensive care units (NICUs) are commonly prescribed antibiotics. As evidence, in a point prevalence study of 29 NICUs, 47% of 827 infants were receiving at least one antibiotic on the day of the survey [1]. Antibiotics are frequently initiated for suspected infection, particularly in low birth weight infants [6]. Biomarkers may be useful to identify infants with true infection and reduce unnecessary antibiotic use. In a multicenter study, Franz *et al.* assessed the impact of measuring interleukin-8 and CRP versus CRP alone on the initiation of empiric antibiotics for EOS and found that the use of both biomarkers and CRP alone decreased antibiotic use (49.6% vs. 36.1%; p<0.0001), and there was not an increase in missed infections [7].

In this study, we hypothesize that the use of antibiotics in late preterms who are asymptomatic but with maternal risk factor (preterm prelabor rupture of membrane [pPROM]) and preterm onset of labor (PTOL) for EOS and in symptomatic neonates but

without maternal risk factor for sepsis can be optimized by not initiating antibiotic at birth.

METHODS

This descriptive study was conducted in a tertiary care center, located in Trivandrum, Kerala. The hospital is recognized for undergraduate and postgraduate training courses under MCI. All late preterm (34^{+0}–36^{+6} weeks) babies with and without maternal risk factor for EOS, and with and without symptoms at birth, delivered in our hospital during the study period (from April 2016 to March 2017) were included in the study. Gestational age of the study neonates was confirmed with early ultrasound done during the first trimester of pregnancy and in those babies with the unavailability of early antenatal ultrasound, New Ballard scoring was done to assess their gestational age. The cause of prematurity of our study neonates are: PTOL, pPROM, severe pregnancy induced hypertension, placenta previa, abnormal Doppler, abruptio placentae, severe oligohydramnios, Indirect Coomb's Test positive, previous caesarian section, breech presentation and twin gestation.

All late preterm neonates (34^{+0}–36^{+6} weeks) who are asymptomatic at birth with and without maternal risk factor for EOS at birth were subjected to clinical assessment of the following: Sensorium, temperature, oxygenation status assessed by the presence of respiratory distress (Downes score), and requirement of oxygen for maintaining saturation (to keep SpO_2 91–95%), perfusion assessed by capillary filling time and skin color, starting after 1 h of initial stabilization till discharge from hospital. Sepsis screen (CRP and absolute neutrophil count [ANC]) was obtained at 24 h and 48 h of age from these asymptomatic late preterms.

Only those babies who had positive sepsis screen or abnormal clinical findings on observation were initiated on antibiotics – injection ampicillin and gentamicin after obtaining blood culture (using BacT/Alert FA microbial detection system). The doses and frequencies of antibiotics were adjusted to gestational age and postnatal age as per the neonatal drug formulary. Antibiotics were stopped with negative sepsis screen and negative blood culture at 48–72 h. None of our symptomatic babies required inotropic or ventilator support while three babies required short period of non-invasive ventilation. All late preterms, who remained asymptomatic during the hospital stay and not initiated on antibiotics, were followed up for 1 month age for any readmission to hospital requiring intravenous (IV) antibiotic with suspect late-onset sepsis.

Late preterm neonates (34^{+0}–36^{+6} weeks) who were symptomatic at birth with and without maternal risk factor for EOS were initiated on antibiotic at birth after obtaining blood culture. Symptoms at birth were defined as the presence of tachypnea (respiratory rate >60/mt), chest retractions, grunting, requiring oxygen through hood or respiratory support, and poor tone and poor activity developed within 4 h of birth.

The study was conducted for 12 months period, so the total number of late preterms delivered during this study period was

included for analysis. The data were entered into the Microsoft Excel sheet and the results were analyzed descriptively using the SPSS statistics version 19. The probabilities of developing late-onset sepsis in those asymptomatic babies and the rate of risk increase in the onset of symptoms in neonates exposed to maternal risk factor for sepsis were calculated.

RESULTS

In this descriptive study, 135 late preterm neonates (34^{+0}–36^{+6} weeks) recruited during the study period were included for analysis. Mean gestational age of the study population was 36 weeks and the mean birth weight was 2340 g. Table 1 shows the cause of prematurity of the study neonates. A total of 116 neonates (86%) were asymptomatic at birth and not initiated on IV antibiotics. Among those 116 asymptomatic babies, 38 babies (33%) were exposed to maternal risk factor (pPROM and/or PTOL) for sepsis and not received IV antibiotics. Serial sepsis screen at 24 and 48 h of age and the blood culture were negative in all babies. Five babies were lost to follow-up and remaining 111 asymptomatic babies were followed up for 1 month, they were clinically remained well and not required hospital admissions necessitating IV antibiotics during the neonatal period.

Of 135 neonates, 19 (14%) were symptomatic at birth. Among those 19 symptomatic babies, only 8 babies (42%) were exposed to maternal risk factor (pPROM and/or PTOL) for sepsis and 11 (58%) babies were not exposed to maternal risk factor for sepsis, but all babies were initiated on IV antibiotics as they were symptomatic (Table 2). Serial sepsis screening and blood culture were negative in all those symptomatic babies, but antibiotics continued for 3–5 days until babies were clinically well. None of those symptomatic babies required inotropic support. 58% of symptomatic babies who were not exposed to maternal risk factor for sepsis received unnecessary antibiotics, even though their sepsis screening and blood culture were negative.

On estimating, the rate of onset of symptoms at birth, in neonates exposed to maternal risk factor for EOS, has shown no statistical

Table 1: Cause of prematurity of the study neonates

Cause of prematurity	Number
Preterm onset of labor	31
pPROM	18
Fetal distress	17
Previous cesarean section	19
Severe PIH	15
Twin gestation	13
Placenta previa	4
Severe oligohydramnios	3
Breech presentation	2
Abruption placenta	1
Abnormal Doppler	1
ICT positive (1:128)	1

pPROM: Preterm prelabor rupture of membranes, PIH: Pregnancy-induced hypertension, ICT: Indirect Coombs test

Table 2: Babies exposed to maternal risk factor for EONS

Number of babies	Maternal risk factor for EOS			p value
	Presence	Absent	Odds ratio (95% CI)	
Symptomatic at birth	8	11	0.66 (0.24–1.8)	0.42
Asymptomatic at birth	38	78		

EONS: Early-onset neonatal sepsis, CI: Confident interval, EOS: Early-onset sepsis

significance in relation to the presence of symptoms at birth odds ratio (OR) 0.66, 95% confident interval (CI) (0.24–1.8) p=0.42.

DISCUSSION

EOS remains a serious and potentially fatal illness. Laboratory tests alone are neither sensitive nor specific enough to guide EOS management decisions. Assessing term and late preterm infants for risk of EOS are one of the most common clinical tasks conducted by pediatric providers [8]. In sick babies, we are posed to treat suspect or proven infection. However, the vast majority of newborn babies who are given antibiotics do not have infection. Widespread use of broad-spectrum antibiotic has been associated with the development of multidrug-resistant Gram-negative bacilli and invasive candidiasis [1]. Sepsis screens are mainly focused on babies who have no symptoms or signs of infection but have risk factors for EOS which are not sufficiently severe to prompt immediate treatment with antibiotics. The purpose of sepsis screen is to distinguish between babies who require a course of antibiotic treatment because the infection is likely or definitely present and in those in whom infection can be ruled out [1].

Puopolo *et al.*, the American Academy of Pediatrics committee on infectious diseases, currently suggested three approaches for the use of risk factors to identify infants who are at increased risk of EOS [9]. Considering maternal risk factor threshold values alone, to identify infants at increased risk of EOS, results in overuse of empirical antibiotics [9]. Researchers at a center in Italy reported a cohort of 7628 term infants, who were managed with a categorical approach (maternal risk factor threshold values alone) to risk identification. The outcomes were then compared with a cohort of 7611 infants who were managed with serial physical examinations of the infant every 4–6 h through 48 h of age. Significant decreases in the use of laboratory tests, blood cultures, and empirical antibiotic agents were observed in the second cohort. Two infants who developed EOS in the second cohort were identified as they developed signs of illness [10]. The primary advantage of this approach is a significant reduction in the rate of antibiotic use.

In our study, we could observe that, if infants were managed based on maternal risk factor alone, it will result in increased use of antibiotics. Furthermore, maternal risk factor for EOS has shown no relation with increase in the presence of symptoms at birth, although it is not statistically significant in this study (OR 0.66, 95% CI: 0.24–1.8). It has been suggested that pediatric providers

should conduct serial clinical evaluations on all newborn infants without regard to the risk of EOS.

According to Puopolo *et al.* [9], a third strategy consists of the reliance on clinical signs of illness to identify infants with EONS. Under this approach, regardless of any estimation of neonatal or maternal risk factors for EONS, infants who appeared to be ill at birth and those who developed signs of illness over the first 48 h after birth are either treated empirically with antibiotic agents or further evaluated by laboratory screening. Among term and late preterm infants, good clinical condition at birth is associated with a reduction in risk for EOS of approximately 60–70% [11,12]. A multidisciplinary panel sponsored by *Eunice Kennedy Shriver* National Institute of Child Health and Human Development advocated that infants be flagged for risk of EOS on the basis of the obstetric diagnosis of suspected intra-amniotic infection but that those conducting newborn evaluation primarily should rely on clinical observation alone for well-appearing term and late preterm infants [13]. The limitation to this study was the small sample size and a study with considerably larger sample size is suggested for comprehensive outcome. In this study, we could observe that even in symptomatic babies with and without maternal risk factor for sepsis, none of the babies had positive blood culture (gold standard). Furthermore, the presence of negative serial sepsis screen (combination of CRP and ANC) along with baby remaining clinically well increased the negative predictive value and helped us to rule out the infection and not missed any infection.

CONCLUSION

In our study, as maternal risk factor for sepsis has shown no statistical significance for the presence of symptoms at birth, antibiotics use can be restricted to only those babies who have clinical worsening over 24–48 h of observation and/or along with supportive evidence of positive sepsis screen and/or blood culture, irrespective of the presence or absence of maternal risk for sepsis. For strong recommendation, the study has to be conducted with large sample size.

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