Pediatric Drugs (2020) 22:321–330
https://doi.org/10.1007/s40272-020-00388-1

ORIGINAL RESEARCH ARTICLE

A Prospective Cohort Study of Factors Associated with Empiric Antibiotic De-escalation in Neonates Suspected with Early Onset Sepsis (EOS)

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Published online: 18 March 2020

Abstract

Background Prolonged empiric antibiotic use, resulting from diagnostic uncertainties, in suspected early onset sepsis (EOS) cases constitutes a significant problem. Unnecessary antibiotic use increases the risk of antibiotic resistance. Furthermore, prolonged antibiotic use increases the risk of mortality and morbidity in neonates. Proactive measures including empiric antibiotic de-escalation are crucial to overcome these problems.

Methods This was a prospective cohort study conducted in the neonatal intensive care units of two public hospitals in Malaysia. Neonates with a gestational age greater than 34 weeks who were started on empiric antibiotics within 72 h of life were screened. The data were then stratified according to de-escalation and non-de-escalation practices, where de-escalation practice was defined as narrowing down or discontinuation of empiric antibiotic within 72 h of treatment.

Results A total of 1045 neonates were screened, and 429 were included. The neonates were then divided based on de-escalation ($n=207$) and non-de-escalation ($n=222$) practices. Neonates under non-de-escalation practices showed significantly longer durations of antibiotic use compared to those under de-escalation practices ($p<0.05$), with no difference in treatment outcomes. Five factors were found to be associated with de-escalation of antibiotics. They are cesarean section delivery, exposure to antenatal steroids, nil history of maternal pyrexia, absence of meconium-stained amniotic fluid, and normal C-reactive protein ≤ 0.5 mg/dL ($p<0.05$).

Conclusions Empiric antibiotic de-escalation appears feasible as a routine form of treatment for EOS in late preterm and term neonates.

1 Introduction

According to the American College of Obstetricians and Gynecologists, group B *Streptococcus* (GBS) prevention guidelines, late preterm and term deliveries accounted for nearly 80% of early onset sepsis (EOS) cases [1, 2]. Management of suspected EOS in late preterm and term neonates varies widely. In currently published guidelines from medical bodies such as the Canadian Paediatric Society, the American Academy for Pediatrics, the National Institute for

Key Points

Empiric antibiotic de-escalation should be encouraged, especially in cases with low suspicion of early onset sepsis (EOS).

Empiric antibiotic de-escalation can be routinely implemented for EOS because of its comparable treatment outcomes to those in neonates without antibiotic de-escalation.

To prevent unnecessary and prolonged antibiotic use, factors associated with antibiotic de-escalation may be used to determine whether antibiotic use should be de-escalated.

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Health and Care Excellence, the Swiss Society of Neonatology, and the Belgian and Flemish Societies of Neonatology and Paediatrics, there is a lack of consensus regarding the best time to review empiric antibiotic treatment for EOS [3]. In Malaysia, disagreements exist between the 4th edition of *Paediatric Protocols* and 3rd edition of the *National Antibiotic Guideline* (NAG), with the time recommended to review empiric treatment in EOS listed as 48–72 h and 36 h, respectively [4–6].

Limited rapid and reliable laboratory sensitivity and specificity, coupled with the non-specific clinical manifestations of EOS pose a challenge regarding the confirmation of an initial diagnosis of sepsis in neonates [7]. Blood culture proof remains the 'gold standard' to diagnose EOS. However, false negatives resulting from blood culture are common among neonates. In previous studies, as few as 5% of treated suspected EOS cases reported a positive blood culture, while 95% of EOS cases were treated without evidence of infection [7, 8]. It is now an acceptable practice for pediatricians to treat EOS in spite of a negative blood culture [9].

Selection of empiric antibiotic therapy should take local microbial susceptibility patterns into consideration [10–12]. In cases with no obvious infection or when blood cultures suggest infection is unlikely, antibiotic de-escalation either by discontinuation or narrowing down the antibiotic spectrum is recommended [13–15]. Such action should be taken within 72 h or as soon as blood culture results are found to be negative [4, 15].

De-escalating continued empiric antibiotic use decreases exposure to antibiotics, consequently preventing resistance development and minimizing cost [15]. However, clinical outcomes resulting from antibiotic de-escalation must be at least comparable to the results from the conventional approach of maintaining initial therapy [15]. De-escalation practices have shown favorable clinical outcomes in adult critical care patients with pneumonia, intra-abdominal infections, and septic shock [13–15]. However, current information on de-escalation of empiric antibiotic use in neonates has been limited or not well described.

In suspected EOS, confirmation of infection by positive blood culture is rarely reported [7, 9]. Therefore, de-escalation of antibiotics within 72 h of initiation remains difficult to achieve for pediatricians. Historically, decision making has been loosely based on blood culture and mostly guided by the pediatrician's judgment [6]. However, it is possible to de-escalate antibiotics in suspected EOS cases, especially in well-appearing neonates with negative blood culture [16].

In a 2014 randomized controlled trial conducted by Pasha et al., neonates of gestational age (GA) $\geq$ 34 weeks with suspected EOS and a negative blood culture were randomized into 3-day and 5-day treatment groups. There were no differences in treatment failure between groups. Treatment failure was defined as the reappearance of sepsis 2 weeks after the discontinuation of treatment [17].

Cordero and Ayers (2003) conducted a study on extremely low birth weight (BW) neonates with an average GA of 25–27 weeks. They found that discontinuation of empiric antibiotics when blood culture was negative for $\leq$ 3 days versus continued for $\geq$ 7 days resulted in desirable treatment outcomes. Furthermore, mortality was not compromised [18]. Therefore, empiric antibiotic de-escalation in suspected EOS can potentially be implemented, despite wide variations in neonatal GA. Further investigations into this area are needed, including a compilation of evidence from our local setting.

The purpose of this study was to compare characteristics and treatment outcomes between neonates under empiric antibiotic de-escalation therapy and neonates without empiric antibiotic de-escalation. Factors associated with empiric antibiotic de-escalation practice in late preterm and term neonates suspected with EOS were also investigated.

2 Methods

This was a prospective observational cohort study conducted at the neonatal intensive care units (NICUs) of two specialist public hospitals in Malaysia. Both NICUs have similar newborn admission rates and were following criteria in the *Paediatric Protocols* (Ministry of Health, Malaysia) [4] for the management of suspected EOS. This is with regards to the initiation of treatment and de-escalation of empiric antibiotic, which was evaluated based on risk factors, laboratory findings, and clinical progress. These NICUs have full-time clinical pharmacists who actively participate in the drug management in neonates. No intervention or interruption of management by the researcher occurred during the study period. To minimize the Hawthorne effect, all frontline practitioners were not informed about the details of the study, including the study design and types of data collected.

Cases were deemed eligible for inclusion if the neonates were born at a GA greater than 34 weeks and were admitted to the NICU with suspected EOS and started with empiric antibiotic within 72 h of life. Neonates who never received empiric antibiotic, received escalated empiric antibiotic within 72 h of treatment, or those who spent less than 72 h in the NICU were excluded. Ethics approval was obtained from the Medical Research and Ethics Committee, Ministry of Health, Malaysia [NMRR-17-1882-36914 (IIR)].

The medical records of all cases admitted within 72 h of life in the two NICUs were prospectively screened from 1 September until 31 December 2017 (hospital A) and 1 January until 30 April 2018 (hospital B). Hospital A and B were public specialist hospitals located in Klang Valley, Malaysia,

and have a similar NICU admission rate per month. Data on eligible cases were collected from patients' electronic and manual medical records. The data included patients' demographic profiles, risk factors (prolonged rupture of membrane > 18 h, maternal pyrexia > 38 °C, maternal high vaginal swab/urine culture positive, history of being a GBS carrier, meconium-stained amniotic fluid, chorioamnionitis, and perinatal asphyxia), clinical manifestations, prescribed antibiotics, types of organisms, de-escalation practices, and treatment outcomes up to 7 days and 28 days of life. Microbiological analyses included blood cultures prior to the commencement of empiric antibiotics.

A late preterm was defined as born between gestational weeks 34 and 36, and term was defined as born at GA 37 weeks and later [19, 20]. Empiric antibiotic de-escalation is defined as narrowing of the antibiotic spectrum by reducing the number of first-line antibiotic combinations (e.g., penicillin/ampicillin plus gentamicin/cefotaxime) or discontinued use of all antibiotics in the absence of any obvious infection within 72 h of therapy [13, 14]. Non-de-escalation is defined as the continuation of first-line empiric antibiotics, especially following negative culture results, based on risk assessment [21]. Treatment failure is defined as the need for late antibiotic escalation after 72 h of empiric antibiotic therapy, strong suspicion of second infection within 7 days of life, or mortality within 7 days of life due to sepsis [22].

Data were stratified according to de-escalation and non–de-escalation practices and were analyzed using IBM® SPSS® for Windows Version 23. The frequencies and percentages of each continuous variable studied were presented in the form of a table. For practice comparison, categorical variables were assessed using Pearson Chi-squared test (χ^2 test) or Fisher's exact test. Continuous variables were assessed using the Mann–Whitney U test, as the medians from both groups were compared. For all statistical analyses, the significance was set at $p < 0.05$. Simple logistic regression was conducted to identify the possible predictors related to de-escalation practice, and variables with p value of < 0.1 were considered for inclusion in a multiple logistic regression analysis using a forward LR method [23].

3 Results

Figure 1 describes the flowchart for the case selection process. A total of 1045 neonates were screened, and 440 neonates fulfilled the inclusion criteria (hospital A = 172, hospital B = 268). However, only 429 neonates were included for analysis, as 11 neonates were excluded due to transfer out from the NICU ($n = 6$) and antibiotic escalation ($n = 5$) within 72 h of treatment. A total of 207 cases were in the de-escalation group (106 cases off one antibiotic and 101 cases off all antibiotics within 72 h), and 222 cases were under the non-de-escalation group.

The demographic and clinical data of cases were compared (Table 1). Births via cesarean sections, exposure to antenatal steroids, and congenital anomalies were all statistically significantly higher in the de-escalation group versus

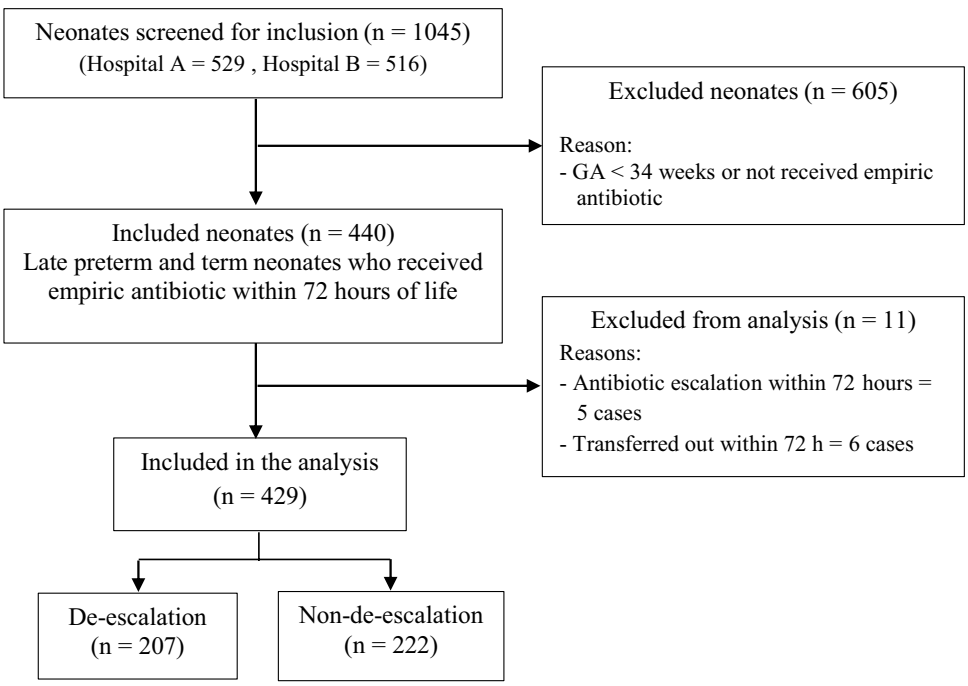

Fig. 1 Flowchart of the selection process for cases within 72 h of empiric antibiotic therapy. *GA* gestational age

Table 1 Demographic, clinical data, and pattern of empiric antibiotic used for EOS ($n=429$)

Characteristics	De-escalation ($n=207$)	Non-de-escalation ($n=222$)	p value
Maternal factors			
Age (years), mean (SD)	29.77 (5.291)	30.01 (4.897)	0.634
Antepartum antibiotic exposure, *n* (%)	14 (6.8)	18 (8.1)	0.606
IAP, *n* (%)	50 (24.2)	74 (33.3)	0.039*
IAP completed ≥ 4 h prior delivery, *n* (%)	40 (19.3)	60 (27.0)	0.881
Cesarean section, *n* (%)	103 (49.8)	53 (23.9)	< 0.001*
Antenatal steroid, *n* (%)	49 (23.7)	17 (7.7)	< 0.001*
Congenital anomalies, *n* (%)	10 (4.8)	3 (1.4)	0.035*
Maternal risk			
PROM > 18 h, *n* (%)	35 (16.9)	46 (20.7)	0.313
Maternal pyrexia > 38 °C, *n* (%)	9 (4.3)	44 (19.8)	< 0.001*
Maternal high vaginal swab/urine culture positive, *n* (%)	19 (9.2)	17 (7.7)	0.570
History of GBS carrier, *n* (%)	2 (1.0)	3 (1.4)	1.000
Meconium-stained amniotic fluid	37 (17.9)	63 (28.4)	0.010*
Chorioamnionitis, *n* (%)	9 (4.3)	44 (19.8)	< 0.001*
Perinatal asphyxia, *n* (%)	5 (2.4)	1 (0.5)	0.111
Neonatal factors			
Gestational age (weeks), mean (SD)	37.37 (2.034)	38.13 (1.803)	< 0.001*
Birth weight (kg), mean (SD)	2.882 (0.680)	3.05 (0.644)	0.011*
Gender			0.999
Male, *n* (%)	124 (59.9)	133 (59.9)	
Female, *n* (%)	83 (40.1)	89 (40.1)	
Race			0.244
Malay, *n* (%)	158 (76.3)	185 (83.3)	
Chinese, *n* (%)	7 (3.4)	7 (3.2)	
Indian, *n* (%)	22 (10.6)	13 (5.9)	
Others, *n* (%)	20 (9.7)	17 (7.7)	
Length of stay (days), *n* (%)			0.613
≤ 7	154 (74.4)	171 (77.0)	
8–27	44 (21.3)	45 (20.3)	
≥ 28	9 (4.3)	6 (2.7)	
Ventilation support, *n* (%)	127 (61.4)	109 (49.1)	< 0.001*
Surfactant, *n* (%)	3 (1.4)	4 (1.8)	0.603
APGAR score at 1 min, mean (SD)	7.46 (2.314)	8.03 (1.725)	0.027
Score ≤ 3, *n* (%)	17 (8.2)	5 (2.3)	0.007*
APGAR score at 5 min, mean (SD)	9.01 (1.885)	9.39 (1.387)	0.061

Table 1 (continued)

Characteristics	De-escalation ($n=207$)	Non-de-escalation ($n=222$)	p value
Score ≤ 3, *n* (%)	6 (2.9)	3 (1.4)	0.291
Clinical sign and symptoms			
Thermoregulatory symptoms, *n* (%)			
Fever	6 (2.9)	10 (4.5)	0.380
Hypothermia	5 (2.4)	2 (0.9)	0.270
Cardiac symptoms, *n* (%)			
Tachycardia	4 (1.9)	6 (2.7)	0.753
Bradycardia	3 (1.4)	0 (0.0)	0.111
Hypotension, *n* (%)	2 (1.0)	7 (3.2)	0.177
Respiratory symptoms, *n* (%)			
(Cyanosis, grunting, recession, tachypnea, nasal flaring)	119 (57.5)	126 (56.8)	0.878
Gastrointestinal symptoms, *n* (%)			
Feeding intolerance	0 (0.0)	6 (2.7)	0.031*
Vomiting	19 (9.2)	13 (5.9)	0.191
Metabolic symptoms, *n* (%)			
Acidosis (first blood gas)	68 (32.9)	51 (23.0)	0.022*
Hypoglycemia	13 (6.3)	7 (3.2)	0.125
Seizure, *n* (%)	3 (1.4)	2 (0.9)	0.676
Abnormal baseline laboratory			
WBC count < 10 or > 26×10^9/L, *n* (%)/total sample, *n* (%)	62 (30.0)/205 (99.0)	69 (31.1)/220 (99.1)	0.803
PLT count < 100 or > 450×10^9/L, *n* (%)/total sample, *n* (%)	10 (4.8)/203 (98.1)	11 (5.0)/219 (98.6)	0.964
CRP > 0.5 mg/dL, *n* (%)/total sample, *n* (%)	9 (4.3)/116 (56.0)	86 (38.7)/169 (76.1)	< 0.001*
Treatment summary			
First dose empiric antibiotic, *n* (%)			0.317
Within 24 h of life	187 (90.3)	190 (85.6)	
Within 48 h of life	16 (7.7)	25 (11.3)	
Within 72 h of life	4 (1.9)	7 (3.2)	
Initial antibiotic combinations, *n* (%)			0.001*
Penicillin + gentamicin	206 (99.5)	201 (90.5)	
Ampicillin + gentamicin	0 (0.0)	1 (0.5)	
Penicillin + gentamicin/cefotaxime	1 (0.5)	20 (9.0)	
Treatment duration (day), median (IQR)	3 (2–3)	5 (4–5)	0.001*

APGAR appearance, pulse, grimace, activity, respiration, *baseline CRP* C-reactive protein taken within 6 h after birth, *baseline PLT* pre-treatment platelet, *baseline WBC* pre-treatment white blood cell, *EOS* early onset sepsis, *GBS* group B *Streptococcus*, *IAP* intrapartum antibiotic prophylaxis, *IQR* interquartile range, *PROM* prolong rupture of membrane, *SD* standard deviation

*Statistically significant at $p<0.05$

the non–de-escalation group. Intrapartum antibiotic prophylaxis (IAP), maternal pyrexia, meconium-stained amniotic fluid, and chorioamnionitis were significantly higher in the non-de-escalation group versus the de-escalation group. Cases in the de-escalation group had significantly smaller mean GA and BW. However, a significantly higher number of cases in the de-escalation group required early ventilator support and presented with poor Appearance, Pulse, Grimace, Activity, Respiration (APGAR) score at 1 min, ≤ 3.

There was no significant difference in the timing of the first dose of empiric antibiotics for both groups. However, there was significant difference in the choice of antibiotics between the groups. The number of cases requiring a switch from gentamicin to cefotaxime was higher in the non–de-escalation group, and this was mostly documented as being for central nervous system antibiotic coverage or due to a suspicion of acute renal impairment. The duration of antibiotic treatment was significantly longer in the non-de-escalation group (Table 1).

Isolated pathogens in blood samples were reported in seven cases (1.6%). Of these cases, the causative organism was gram positive in five cases. Three of the pathogens were responsible for clinically significant infections with raised C-reactive protein (CRP) > 0.5 mg/dL (GBS, *Listeria monocytogenes*, and *Klebsiella* sp.), and other isolated pathogens were labeled as 'contaminant sample' in the pathology report. Antibiotic sensitivity showed *Klebsiella* sp. and *Sphingomonas* (*pseudo.*) *paucimobilis* were sensitive to gentamicin, while *L. monocytogenes* was sensitive to penicillin (Table 2).

Table 3 shows the treatment outcomes up to 7 days and 28 days of life. There was no significant difference in treatment failure levels between both groups. The cause of mortality within 7 days of life was not stated as sepsis (two cases of persistent pulmonary hypertension of the newborn and one case of hydrops fetalis) and therefore was not categorized as treatment failure. Treatment outcomes up to 28 days of life included a high number of suspicions of second infection and mortality after 7 days of life in de-escalation group versus the non-de-escalation group. However, the difference was not statistically significant.

Identified factors with a $p < 0.1$ based on univariate analysis were exposure to IAP, cesarean section delivery, exposure to antenatal steroids, congenital anomalies, maternal pyrexia, meconium-stained amniotic fluid, chorioamnionitis, GA, BW, ventilator support, surfactant, poor APGAR score at 1 min, acidosis, and CRP > 0.5 mg/dL. The identified factors were included in the multivariate analysis. Based on the multivariate analysis model, cesarean section delivery, exposure to antenatal steroids, nil history of maternal pyrexia,

Table 2 Clinical characteristics of neonates showing causative organism isolated in blood sample ($n = 7$)

Case	GA; BW	Pathogens; laboratory	EOS risk factors	Reason for EOS evaluation	Treatment description
De-escalation					
1	39; 3.16	*Cellulomonas* sp.; WBC 15.3, PLT 280, CRP 0.02	PROM > 18 h	Well-appearing neonate, evaluated because of risk factors	Gentamicin 2 doses Penicillin 10 doses Treatment duration: 5 days
2	39; 2.9	Group B *Streptococcus*; WBC 4.4, PLT 214, CRP 7.9	Meconium-stained amniotic fluid	Respiratory distress at birth with tachycardia	Gentamicin 2 doses Penicillin 20 doses Treatment duration: 10 days
3	36; 2.23	*Bacillus* sp.; WBC 16.2, PLT 275, CRP 0.02	Premature with low BW	Hypoglycemia	Gentamicin 2 doses Penicillin 10 doses Treatment duration: 5 days
4	37; 3.24	*Sphingomonas* (*pseudo.*) *paucimobilis*; WBC 27.3, PLT 218, CRP 0.02	None	Respiratory distress at birth	Gentamicin 2 doses Penicillin 14 doses Treatment duration: 7 days
5	37; 3.87	*Staphylococcus,* coagulase negative; WBC 25.9, PLT 268, CRP 0.06	None	Respiratory distress at birth	Gentamicin 2 doses Penicillin 10 doses Treatment duration: 5 days
Non-de-escalation					
6	35; 2.28	*Listeria monocytogenes*; WBC 20.7, PLT 199, CRP 3.8	Meconium-stained amniotic fluid	Respiratory distress with acidosis	Gentamicin 6 doses Penicillin 18 doses Treatment duration: 9 days
7	39; 3.4	*Klebsiella* sp.; WBC 16.3, PLT 160, CRP 10.29	PROM > 18 h Positive maternal culture	Well-appearing neonate, evaluated because of risk factors	Gentamicin 1 dose Cefotaxime 14 doses Penicillin 19 doses Treatment duration: 6 days

BW birth weight, *CRP* C-reactive protein, *EOS* early onset neonatal sepsis, *GA* gestational age, *PLT* platelet, *PROM* prolong rupture of membrane, *WBC* white blood cell

Table 3 Treatment outcomes with antibiotic use for EOS ($n=429$)

	De-escalation ($n=207$)	Non-de-escalation ($n=222$)	p value
Outcomes up to 7 days of life			
Treatment failure, *n* (%)	14 (6.8)	12 (5.4)	0.556
Antibiotic escalation after 72 h, *n* (%)	7 (3.4)	10 (4.5)	
Suspicion of second infection within 7 days of life, *n* (%)	7 (3.4)	2 (0.9)	
Mortality within 7 days of life, *n*	2 (1.0)	1 (0.5)	0.348
Outcomes up to 28 days of life			
Status at the end of follow-up			0.359
Awaiting growth, *n* (%)	4 (1.9)	3 (1.4)	
Survived to discharge, *n* (%)	191 (92.3)	213 (95.9)	
Suspicion of second infection after 7 days of life, *n* (%)	8 (3.9)	3 (1.4)	
Mortality, *n* (%)	6 (2.9)	2 (0.9)	
Others, *n* (%)	6 (2.9)	4 (1.8)	

EOS early onset sepsis

Table 4 Factors associated with antibiotic de-escalation practice among late preterm and term neonates in suspected EOS

Variables	Crude OR (95% CI)[a]	Beta	Adjusted OR (95% CI)[b]	p value[b]
Cesarean section delivery	3.19 (2.11–4.82)	1.27	3.54 (1.93–6.51)	< 0.001*
Antenatal steroids	3.75 (2.10–6.75)	0.87	2.40 (1.04–5.55)	0.041*
No maternal pyrexia > 38 °C	5.44 (2.58–11.46)	1.35	3.85 (1.55–9.60)	0.004*
No meconium-stained amniotic fluid	1.82 (1.15–2.88)	0.74	2.10 (1.07–4.12)	0.030*
Normal baseline C-reactive protein ≤ 0.5 mg/dL	7.38 (3.91–13.95)	2.14	8.51 (4.23–17.15)	< 0.001*

CI confidence interval, *EOS* early onset sepsis, *OR* odds ratio

*Statistically significant at $p<0.05$

[a]Simple logistic regression

[b]Multiple logistic regression

absence of meconium-stained amniotic fluid, and normal baseline CRP ≤ 0.5 mg/dL were factors significantly associated with de-escalation practice (Table 4).

4 Discussion

In spite of the low incidence of culture-proven infection, the continued overuse of antibiotics to treat late preterm and term neonates with suspected EOS drove the desire to evaluate such a practice in our local setting [3]. In this study, we found that slightly over 40% of total admitted neonates were started on empiric antibiotics. Nearly half of them underwent empiric antibiotic de-escalation within 72 h, while the remaining patients continued treatment beyond 72 h. Antibiotic de-escalation was not protocolized practice and was performed by the physician in charge of the patient in accordance with the patient's clinical evolution and other investigations [21]. Thus, the de-escalation rate may vary between hospitals. Currently, no study has reported on the antibiotic de-escalation rate among neonates suspected with EOS. However, in adults, the antibiotic de-escalation rate was reported to be 51% in generally ill patients and ranging from 6 to 74% in ventilator-associated pneumonia patients [21].

In this study, antibiotic practice was guided by the National Antibiotic Guidelines (2019). According to this guideline, in the management of suspected EOS, if blood culture is negative and initial clinical suspicion is not strong, antibiotic de-escalation should be considered at 48 h of treatment after reassuring neonate condition with low CRP. However, if blood culture is positive or there is a strong clinical suspicion of sepsis with a negative blood culture, treatment may be given up to 5–7 days [5].

This study showed similar characteristics for the neonates in both groups (de-escalation and non-de-escalation). These include average GA > 37 weeks, normal BW > 2.5 kg, and similar gender and race distributions, with no significant difference in length of hospital stay. Respiratory-related symptoms such as cyanosis, grunting, recession, tachypnea, and nasal flaring were the most common manifestations documented in both groups. However, clinical manifestations

alone were too non-specific to determine true infections in EOS. Further clinical investigations were needed to confirm EOS [1, 7].

In this study, the majority of suspected EOS cases were started on empiric antibiotic penicillin plus gentamicin within 24 h, in concordance with the national guidelines [4, 5]. To reduce the risks of mortality and morbidity, once EOS is suspected, it is crucial to start empiric antibiotics immediately [24–26]. A higher number of cases requiring change of antibiotic regime from penicillin plus gentamicin to penicillin plus cefotaxime was observed in the non-de-escalation group in our study.

Cefotaxime is a third-generation cephalosporin and is listed as an alternative first-line antibiotic in the NAG [5]. Most of the changes were due to suspected acute renal impairment, which can be worsened by gentamicin administration. However, studies have shown that gentamicin's nephrotoxic effect is less frequent in neonates than in adults [27]. Severe cases of EOS require antibiotics with extensive coverage and excellent cerebrospinal fluid penetration properties. Therefore, cefotaxime is an antibiotic of choice. However, cefotaxime use should be restricted due to rapid development of resistance and risk of invasive candidiasis if routinely used for the treatment of EOS [1]. In this study, less than 5% of the total neonates analyzed were exposed to cefotaxime and none of them developed resistance or candidiasis during their NICU stay.

Besides that, neonates in the non-de-escalation group also reported significantly longer durations of antibiotic use. However, previous studies reported that shorter treatment duration in suspected EOS did not increase the risk of late-onset sepsis, treatment failure, necrotizing enterocolitis or mortality [17, 18, 28]. Similarly, no difference in the frequency of treatment failure was observed in our study.

Overall, positive blood culture was reported in less than 2% of total cases in our study. Furthermore, five out of seven pathogens isolated were gram-positive organisms. These results are in line with those obtained from previous studies conducted in Malaysia, Estonia, and the United States, in which positive blood culture was obtained in < 5% of the study population, was rarely reported, and around 70% of causative pathogens were gram positive [29–33]. False-negative blood culture is common in the neonatal population, possibly due to insufficient blood sample volumes [34] or low-density bacteremia due to perinatal antibiotic exposure [35]. As a result, treating EOS in the presence of a negative blood culture remains the normal practice [9, 36, 37]. However, using blood culture to confirm the diagnosis of EOS remains the 'gold standard.' In the future, more advanced methods such as polymerase chain reaction (PCR) may be useful to improve the EOS diagnosis sensitivity [38].

In our final model, five predictors were identified to be associated with antibiotic de-escalation within 72 h of therapy. They are cesarean section delivery, exposure to antenatal steroids, nil history of maternal pyrexia, absence of meconium-stained amniotic fluid, and normal baseline CRP. A cesarean section delivery was classified as a clean-contaminated operation, with a risk of infection and endometritis to the operative mother, but no additional risk of EOS to the neonate, since there was no contact with the birth canal during the delivery process [39, 40]. Exposure to antenatal steroids was also a predictive indicator for de-escalation practice. To accelerate fetal lung maturation and improve neonatal respiratory function upon delivery, antenatal steroids are given to mothers at risk of premature delivery or elective cesarean before 38 weeks gestation [41]. A study by Gyamfi-Bannerman et al. (2016) at the Maternal–Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development reported that completing two doses of antenatal steroids was not associated with an increased risk of EOS [42].

In this study, there were two maternal risk factors associated with antibiotic de-escalation practice. They are nil history of maternal pyrexia and absence of meconium-stained amniotic fluid. Maternal pyrexia is a risk factor listed in most guidelines and is a criterion to start empiric antibiotic therapy [16, 43]. Nonetheless, previous studies reported that only about 6.4% of evaluated neonates were infected when the maternal recorded temperature was 38.9 °C, with reduced risk as temperature drops [16, 43, 44]. Meconium-stained amniotic fluid was not considered as a criterion to start empiric antibiotics, as meconium aspiration syndrome presented in only 5% of meconium-stained amniotic fluid cases [45, 46]. Therefore, if neonates are clinically well without risks of maternal pyrexia and meconium-stained amniotic fluid, empiric antibiotics de-escalation can safely be implemented.

A normal baseline level of CRP was identified as a predictor for antibiotics de-escalation in our study. It is a widely used biomarker with a high specificity. However, it has a low sensitivity for indicating neonatal sepsis, as its levels rise in non-infectious events as well [47, 48]. CRP concentration may appear normal in the early stage of infection, and it has limited predictive value in the single figures, due to physiological variations in the first few days of life [7]. Serial CRP in the first 24–48 h of symptoms increases test sensitivity and can be helpful in determining the duration of empiric antibiotic use [7, 16, 49, 50]. However, in this study, serial CRP to guide treatment decisions was not a routine practice.

This study had some limitations because de-escalation or non-de-escalation practices were based on clinician preference and involved only two public hospitals. Therefore, results cannot be generalized. Besides, this study did not use the Kaiser risk assessment calculator to determine whether an antibiotic should be started for EOS [51]. Instead, the criteria used was based on our local reference *Paediatric*

Protocols (4th edition) as this was the reference commonly used by the physicians at our study sites. Hence, there could be a possibility that an antibiotic was started even though the EOS risk was low according to the Kaiser risk assessment. It is not surprising that most of the identified factors in this study are factors currently included in the Kaiser risk assessment. Despite the limitations, to our knowledge, this is the first local study investigating factors associated with empiric antibiotic de-escalation among neonates with suspected EOS.

In conclusion, this study demonstrated that among late preterm and term neonates suspected with EOS, strategic empiric antibiotic de-escalation was possible in most cases, without any negative impact on clinical outcomes.

Acknowledgements We (the authors) would like to thank the Director-General of Health Malaysia for the permission to publish this paper. We are grateful to Dr. See Kwee Ching, Consultant Neonatologist of Sungai Buloh Hospital and Head of Pediatric Department Hospital Shah Alam for their support toward this research project. We are also thankful to Faculty of Pharmacy Universiti Kebangsaan Malaysia, Pharmacy Department and Neonatal Intensive Care Unit of Sungai Buloh Hospital and Hospital Shah Alam for their technical support.

Compliance with Ethical Standards

Funding None.

Conflict of interest The authors, Nazedah Ain Ibrahim, Mohd Makmor Bakry, Nurul Ain Mohd Tahir, Nur Rashidah Mohd Zaini, and Noraida Mohamed Shah, declare that they have no conflicts of interest.

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