JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Exploring the potential impact of empiric antibiotic de-escalation for suspected early onset neonatal sepsis

Nazedah Ain Ibrahim[1,2], Mohd Makmor Bakry[1], Shareena Ishak[3], Nurul Ain Mohd Tahir[1], Noraida Mohamed Shah[1]

[1] Centre for Quality Management of Medicines, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia
[2] Department of Pharmacy, Hospital Tunku Azizah, Ministry of Health, 50300 Kuala Lumpur, Malaysia
[3]Department of Pediatrics, Faculty of Medicine Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, 56000 Bandar Tun Razak, Cheras, Kuala Lumpur, Malaysia

Abstract

Introduction: The aim of this study was to explore the impact of empiric antibiotic de-escalation for suspected early onset neonatal sepsis (EONS) on clinical and economic outcomes. This was a multicenter prospective cohort study. Newborns were recruited from 3 neonatal intensive care units (NICUs) in Klang Valley, Malaysia.

Methodology: All newborns in the NICU, and prescribed with empiric antibiotics within 72 hours for EONS over 4 months were included. Data on newborns' characteristics, clinical outcomes, cost-effectiveness in 7 days, and mortality in 28 days were recorded. Antibiotic usage was divided into de-escalation and non-de-escalation groups, with 1:1 data matching for gestational age (weeks) and birth weight (± 0.1 kg). Time to treatment success, 28-days all-cause mortality, and cost-effectiveness were analyzed.

Results: A total of 687 newborns were included. Data matching was conducted for grouping into de-escalation and non-de-escalation groups (n = 262 per group) for comparative analysis. There was no significant difference in the treatment failure rate ($p = 0.742$) and all-cause mortality in 28-days of life ($p = 0.052$) between the groups. However, a significant difference in terms of time to treatment success (median 3 days in the de-escalation group vs. 5 days in the non-de-escalation group; $p < 0.001$)) was observed. Cost-effectiveness analysis showed cost-saving of USD 47.80 per newborn per day for the de-escalation group.

Conclusions: Early empiric antibiotic de-escalation should be considered in all newborns with a low risk of EONS. This practice did not increase the treatment failure rate and provided a beneficial outcome.

Key words: neonatal; early onset sepsis; antibiotic; de-escalation.

J Infect Dev Ctries 2025; 19(6):896-903. doi:10.3855/jidc.20654

(Received 30 July 2024 – Accepted 18 November 2024)

Introduction

Newborns are often exposed to antibiotics in the neonatal intensive care units (NICU) [1]. Timely treatment with empirical antibiotics in newborns with suspected early onset neonatal sepsis (EONS) is crucial for achieving optimal treatment outcomes and reducing the risk of mortality [2]. However, if long-term empiric antibiotic treatment is administered to an infection-free newborn, it may lead to adverse effects such as increased risk of late sepsis infection, necrotizing enterocolitis (NEC), and mortality [3].

One of the major challenges in the management of suspected EONS is determining the duration of empirical antibiotic treatment. Using blood culture alone to guide the practice of antibiotic de-escalation or escalation is inadequate due to its low sensitivity [4]. Antimicrobial stewardship programs (AMS) have been implemented in the NICUs globally to optimize antibiotic usage [1]. The AMS program is an important activity in the era of increasing bacterial resistance and absence of novel antibiotics [5].

Antibiotic de-escalation is an important strategy in AMS, either by minimizing the number of antibiotics used or by stopping treatment immediately when there are no clear signs of infection [6]. In general, implementation of the AMS program has been proven to significantly reduce antibiotic use and total treatment costs [7]. Antibiotic de-escalation strategies also showed no increment in the risk of mortality among adult patients in the intensive care unit (ICU) [8]; and reduced treatment costs, risk of adverse effects, and bacterial resistance through antibiotic selective pressure and superinfection [9,10].

The most common antibiotic de-escalation effects reported in previous studies were shorter hospitalization periods; shorter time for optimal therapeutic effect or

duration of treatment; and reduction of cost of treatment, mortality rate, and risk of antibiotic resistance [9–12]. Most antibiotic de-escalation studies reported that de-escalation practices reduced the duration of hospital stay and did not increase mortality rates. These studies were performed among adult populations in the ICU or among patients with serious clinical conditions [13–15].

The effects of antibiotic de-escalation practice on neonatal populations are still poorly studied and reported. The antibiotic de-escalation strategy seems to be important in the management of suspected EONS, as the yield for positive blood culture to guide treatment duration is scarce. A randomized controlled trial conducted in Iran and a prospective observational study conducted in the United States of America compared the antibiotic duration of ≤ 3 days vs. ≥ 5 and 7 days, respectively, for the treatment of suspected EONS. Both studies showed that there was no difference in treatment failure and mortality rate between the groups with negative blood cultures [16,17].

Immediate de-escalation practice should be considered in newborns with negative blood culture results who are clinically stable and without signs of active infection within 72 hours of empirical antibiotic treatment [18,19]. More studies are needed to explore the impact of empirical antibiotic de-escalation on the clinical and economic outcomes, especially for suspected EONS. The purpose of this study was to descriptively compare time to treatment success, 28-day all-cause mortality, and cost-effectiveness evaluation between empirical antibiotic de-escalation and non-de-escalation groups.

Methodology

This was a prospective observational cohort study involving NICUs of three government and university hospitals in Klang Valley in Malaysia. Ethical approval was obtained from the Medical Research and Ethics Committee of the Ministry of Health Malaysia (NMRR-17-1882-36914 (IIR)) and the Ethics Committee of the Universiti Kebangsaan Malaysia (UKM PP/111/8/JEP-2018-036).

Newborns were eligible to be enrolled if they were admitted to the NICU and had empiric antibiotics commenced within 72 hours of birth based on the assessment of maternal risk factors, clinical presentation, and laboratory findings in accordance with the recommendation in the pediatric protocol [19]. Clinical data of eligible newborns were retrieved from patients' medical records. The data included were demographic profiles, risk factors, clinical presentation, laboratory results, empiric antibiotics prescribed, treatment outcomes at 7 days of life, and mortality at 28 days of life.

Newborns were further classified into de-escalation and non-de-escalation groups. De-escalation was defined as the discontinuation of one or all antibiotics within 72 hours after initiation. Non-de-escalation was defined as the continuation of the antibiotics beyond 72 hours after initiation [20]. Newborns who were transferred out from the NICU, died, or experienced an escalation of antibiotics within 72 hours of treatment were excluded.

Newborns in the de-escalation and non-de-escalation groups underwent a data matching process using the Microsoft® Excel software based on their gestational age (same gestational week) and birth weight (± 0.1 kg) with a 1:1 ratio. This process was carried out to ensure that both groups with similar characteristics were compared [21–24].

The total medical costs evaluated were ward charges, staff salary, laboratory costs, and antibiotic costs (Supplementary Table 1). Information regarding ward charges and laboratory costs was obtained from the Fees (Medical) Act price list, which are standard charges used in Malaysian public hospitals. The minimum salary of staff (doctors and nurses) per 5 newborns per day was obtained from the Public Service Commission website [25] and the costs of antibiotics were the contract price obtained from the public hospital pharmacy logistics office. Data used in calculating overall costs were duration of hospitalization and treatment period. The costs were calculated up to 7 days after birth or until discharge if less than 7 days.

Each of these costs were calculated using the Ringgit Malaysia (RM) currency from the healthcare providers' perspective. This was then converted to the United States Dollar (USD) with a rate of 1 USD = RM 4.1325.

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows software, Version 23.0 (IBM Corp., Armonk, NY, USA). Categorical data were reported as frequency and percentage, while continuous data were reported as mean (standard deviation, SD) or median (interquartile range, IQR). The Mann-Whitney U test was conducted to identify the median significant difference between the de-escalation and non-de-escalation groups for continuous data, while the Pearson Chi square (χ^2) or Fisher's exact test was used to determine significant differences in categorical data between the two groups. In all statistical analyses, $p <$

0.05 was considered statistically significant.

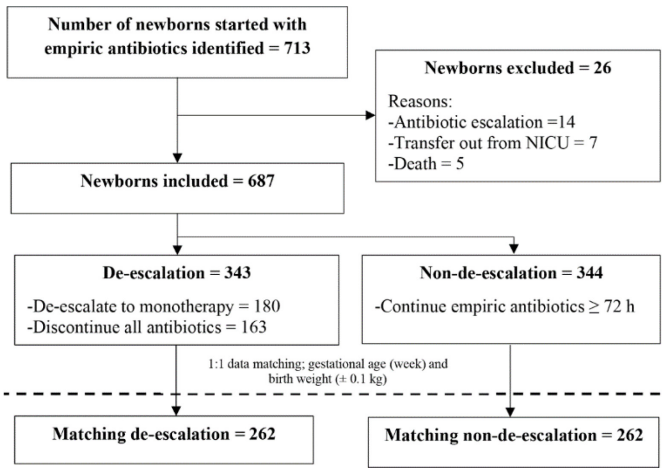
Empirical antibiotic treatment was considered a failure if: (i) mortality occurred within 7 days of birth due to sepsis; (ii) sepsis relapsed within 7 days after empirical antibiotic treatment stopped; or (iii) antibiotic escalation occurred after 72 hours of treatment [26]. Kaplan-Meier analysis was performed using treatment duration and treatment success rate data to assess the clinical effects of de-escalation practice on EONS. The results were tabulated and presented as the time to treatment success curve. Kaplan-Meier survival analysis was performed to assess mortality rates of all causes within 28 days of life for both groups, and the results were reported in the form of tabulated data and 28-day survival curves.

The effect of de-escalation on costs was analyzed using overall costs up to 7 days of hospitalization. Cumulative cost analysis for each group over a period of 7 days was carried out and reported graphically. The incremental cost-effectiveness ratio (ICER) was calculated using an average treatment cost per newborn successfully treated (in RM, then converted to USD) and the time required to achieve optimal therapy (in days) [27]. Time to optimal therapy was defined as the duration needed to achieve treatment success [9].

Results

During the study period, 713 newborns were started on empiric antibiotics within 72 hours after birth. A total of 687 newborns were included and classified into de-escalation and non-de-escalation groups depending on their antibiotic practices within 72 hours of treatment. 163 non-matching newborns were excluded

Figure 1. Selection process and data matching.



based on the closest matching of gestational age and birth weight. The remaining 524 newborns were matched and included in the comparative analysis (Figure 1).

The demographics, risk factors, clinical presentation, laboratory, pattern of empiric antibiotics, and treatment outcomes between de-escalation and non-de-escalation groups are summarized in Table 1. There were significant differences in maternal characteristics whereby the cases of cesarean delivery and incomplete antenatal appointments were higher in the de-escalation group compared to the non-de-escalation group ($p < 0.05$). There was a significantly higher number of maternal exposures to intrapartum antibiotic prophylaxis, advanced maternal age of > 35 years, maternal fever, maternal history of Group B

Table 1. Demographics, clinical presentations, pattern of antibiotics usage and outcome in suspected early onset neonatal sepsis (EONS) (N = 524).

Characteristics	De-escalation n = 262	Non-de-escalation n = 262	*p* value
A. Maternal			
Age (years), mean (SD)	29.93 (5.41)	31.08 (5.14)	0.020*
Advanced maternal age (≥ 35 years), n (%)	47 (17.9)	65 (24.8)	0.058
Cesarean section, n (%)	139 (53.1)	96 (36.6)	0.001*
Antepartum antibiotic exposure (AAE), n (%)	23 (8.8)	23 (8.8)	0.989
Intrapartum antibiotic prophylaxis (IAP), n (%)	57 (21.8)	87 (33.2)	0.004*
IAP completed > 4 hours prior delivery, n (%)	43 (16.4)	65 (24.8)	0.984
Born before arrival/out born, n (%)	14 (5.3)	18 (6.9)	0.472
Antenatal steroid, n (%)	81 (30.9)	66 (25.2)	0.354
Completed 2 doses, n (%)	53 (20.1)	46 (17.6)	0.422
Multiple pregnancies, n (%)	139 (53.1)	147 (56.1)	0.482
Lack of antenatal care, n (%)	27 (10.3)	12 (4.6)	0.012*
Maternal risk			
Prolonged rupture of membranes (PROM) > 18 hours, n (%)	44 (16.8)	54 (20.6)	0.263
Maternal pyrexia > 38 °C, n (%)	10 (3.8)	35 (13.4)	0.001*
Maternal high vaginal swab/ urine culture positive, n (%)	29 (11.1)	26 (9.9)	0.669
History of group B streptococcus (GBS) carrier, n (%)	2 (0.8)	12 (4.6)	0.012[a]*
Meconium-stained amniotic fluid (MSAF)/foul smelling liquor, n (%)	42 (16.0)	54 (20.6)	0.175
Chorioamnionitis, n (%)	9 (3.4)	32 (12.2)	0.001*
Perinatal asphyxia, n (%)	5 (1.9)	2 (0.8)	0.450[a]

Table 1 (*continued*). Demographics, clinical presentations, pattern of antibiotics usage and outcome in suspected early onset neonatal sepsis (EONS) (N = 524).

Characteristics	De-escalation n = 262	Non-de-escalation n = 262	*p* value
B. Neonatal			
Gestational age (week), mean (SD)	36.16 (3.33)	36.16 (3.33)	1.000
Premature (< 36 week), n (%)	113 (43.1)	113 (43.1)	
Term (≥ 37 week), n (%)	149 (56.9)	149 (56.9)	
Birth weight (kg), mean (SD)	2.61 (0.83)	2.64 (0.83)	0.732
< 2.5 kg, n (%)	111 (42.4)	101 (38.5)	
≥ 2.5 kg, n (%)	151 (57.6)	161 (61.5)	
Gender			
Male, n (%)	148 (56.5)	151 (57.6)	0.791
Female, n (%)	114 (43.5)	111 (42.4)	
Race			
Malay, n (%)	202 (77.1)	210 (89.2)	0.281
Chinese, n (%)	11 (4.2)	17 (6.5)	
Indian, n (%)	25 (9.5)	17 (6.6)	
Others, n (%)	24 (9.2)	18 (6.9)	
Length (cm), mean (SD)	48.20 (5.94)	47.11 (5.12)	0.009[b]*
Head circumference (cm), mean (SD)	31.96 (3.27)	31.73 (2.77)	0.504[b]
Length of stay (days), n (%)			
0–7 days	160 (61.1)	142 (54.2)	0.259
8–27 days	69 (26.3)	78 (29.8)	
≥ 28 days	33 (12.6)	42 (16.0)	
Ventilation support, n (%)			0.007*
Intubated	49 (18.7)	79 (30.2)	
Not intubated	121 (46.2)	96 (36.6)	
No ventilation support	91 (34.7)	87 (33.2)	
Surfactant, n (%)	14 (5.3)	31 (11.8)	0.018*
APGAR score @ 1 min, mean (SD)	7.44 (2.28)	7.76 (1.87)	0.552[b]
Score ≤ 5, n (%)	60 (22.9)	36 (13.7)	0.011*
APGAR score @ 5 min, mean (SD)	9.01 (1.88)	9.18 (1.43)	0.676
Score ≤ 5, n (%)	18 (6.9)	7 (2.7)	0.029*
Congenital anomalies, n (%)	14 (5.3)	14 (5.3)	0.992
C. Clinical presentation			
Thermoregulatory symptoms, n (%)			
Fever	6 (2.3)	4 (1.5)	0.752[a]
Hypothermia	8 (3.1)	8 (3.1)	1.000
Cardiac symptoms, n (%)			
Tachycardia	7 (2.7)	17 (6.5)	0.037*
Bradycardia	5 (1.9)	3 (1.1)	0.724*
Hypotension, n (%)	4 (1.5)	12 (4.6)	0.072[a]
Respiratory symptoms, n (%)	155 (59.2)	171 (65.3)	0.149
Cyanosis	16 (6.1)	13 (5.0)	0.567
Grunting	53 (20.2)	82 (31.3)	0.004*
Recession	109 (41.6)	132 (50.4)	0.044*
Tachypnea	64 (24.4)	94 (35.9)	0.004*
Nasal flaring	78 (29.8)	66 (25.2)	0.240
Gastrointestinal symptoms, n (%)			
Feeding intolerance	1 (0.4)	5 (1.9)	0.216[a]
Vomiting	18 (6.9)	10 (3.8)	0.120
Metabolic symptoms, n (%)			
Acidosis	83 (31.7)	65 (24.8)	0.081
Hypoglycemia	15 (5.7)	9 (3.4)	0.210
Seizure, n (%)	4 (1.5)	2 (0.8)	0.686[a]
D. Laboratory			
White blood cells (WBC), mean (SD)	17.92 (8.19)	18.59 (8.97)	
Below < 10 x 10^9/L, n (%)	49 (18.7)	40 (15.3)	0.534
Above > 26 x 10^9/L, n (%)	43 (16.4)	48 (18.3)	
Normal 10–26 x 10^9/L, n (%)	168 (64.1)	173 (66.0)	
Platelet, mean (SD)	240.55 (80.48)	262.12 (84.42)	
Platelet < 100 x 10^9/L)	10 (3.8)	11 (4.2)	0.838
C reactive protein (CRP), mean (SD)	0.37 (1.73)	0.96 (1.81)	
CRP > 0.5 mg/dL	10 (3.8)	68 (26.0)	0.001*
Positive blood culture, n (%)	6 (2.3)	3 (1.2)	0.504
Gram-positive strain	5 (1.9)	2 (0.8)	
Bacillus sp.	2 (0.8)	0 (0.0)	
Group B *streptococcus*	1 (0.4) ^	1 (0.4) ^	

Table 1 (*continued*). Demographics, clinical presentations, pattern of antibiotics usage and outcome in suspected early onset neonatal sepsis (EONS) (N = 524).

Characteristics	De-escalation n = 262	Non-de-escalation n = 262	*p* value
Staphylococcus, coagulase negative	1 (0.4)	0 (0.0)	
Cellulomonas sp.	1 (0.4)	0 (0.0)	
Listeria monocytogenes	0 (0.0)	1 (0.4) ^	
Gram-negative strain	1 (0.4)	1 (0.4)	
Sphingomonas (pseudo.) paucimobilis	1 (0.4)	0 (0.0)	
Klebsiella sp.	0 (0.0)	1 (0.4) ^	
E. Empiric antibiotic pattern			
First dose empiric antibiotic, n (%)			0.843[a]
≤ 24 hours of life	241 (92.0)	239 (91.2)	
25–48 hours of life	16 (6.1)	16 (6.1)	
49–72 hours of life	5 (1.9)	7 (2.7)	
Antibiotic combinations, n (%)			0.001*
Penicillin + Gentamicin	252 (96.2)	232 (88.5)	
Penicillin + Amikacin	5 (1.9)	0 (0.0)	
Penicillin + Cefotaxime	2 (0.8)	1 (0.4)	
Ampicillin + Gentamicin	3 (1.1)	2 (0.8)	
Ampicillin + Cefotaxime	0 (0.0)	1 (0.4)	
Penicillin + Gentamicin/Cefotaxime	0 (0.0)	25 (9.5)	
Meropenem	0 (0.0)	1 (0.4)	
Treatment duration (day), median (IQR)	3 (2-3.5)	5 (4-5)	0.001[b]*
F. Treatment outcome in 7 days of life			
Treatment failure, n (%)	21 (8.0)	19 (7.3)	0.742
Mortality due to sepsis	1 (0.4)	1 (0.4)	1.000
Sepsis relapse	13 (5.0)	4 (1.5)	0.045*
Escalation after 72 hours of empiric antibiotics	8 (3.1)	15 (5.7)	0.136

APGAR: appearance, pulse, grimace, activity, respiration; SD: standard deviation; IQR: interquartile range. ^ clinically significant infection; [a]Fisher's exact test; [b]Mann Whitney U-test; **p* value < 0.05.

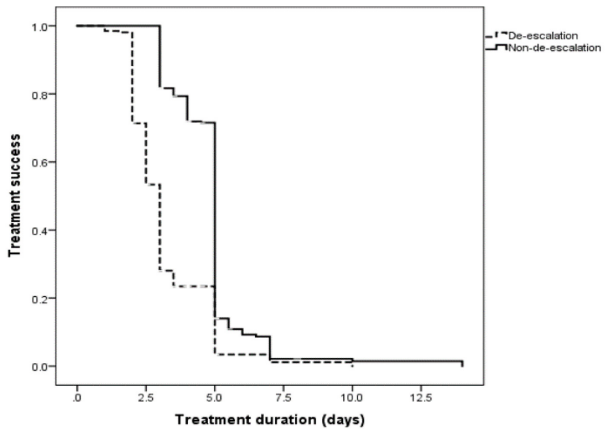
Streptococcus (GBS) infection, and chorioamnionitis in the non-de-escalation group, compared to the de-escalation group ($p < 0.05$).

Significantly more newborns in the non-de-escalation group had early intubation and received intratracheal surfactant therapy. Clinical signs of sepsis, such as tachycardia, grunting, chest recession, and tachypnea, were seen in a significantly higher number of newborns in the non-de-escalation group. The C reactive protein (CRP) level was also notably elevated in the non-de-escalation group. There were significant differences in the choice of empiric antibiotic combination and duration of treatment between the two groups. Further stratified analysis based on clinical severity was conducted by numerically scoring each of the risk and clinical presentations; the results showed no significant differences between both groups with $p > 0.05$.

Ten percent of newborns in the non-de-escalation group had their antibiotic changed from gentamycin to cefotaxime within 72 hours of treatment. Newborns in the de-escalation group had a significantly shorter median treatment period of 3 days, compared to those in the non-de-escalation group (5 days).

Figure 2 shows the treatment success analysis for the de-escalation and non-de-escalation groups. The treatment success rate was over 92% for both groups. The Kaplan-Meier analysis of the time to treatment success showed significant differences between groups in which the de-escalation group required a shorter period (3 days) to complete the treatment successfully as compared to the non-de-escalation group (5 days). The result of this analysis is summarized graphically whereby the curvature of the de-escalation treatment period is a more rapid decrease than the non-de-

Figure 2. The difference in time to treatment success between de-escalation and non-de-escalation groups (N = 524).



Variables	n	Success (%)	Median (95% CI) (days)	Log Rank[a] (df)	*p* value[a]
De-escalation	262	241 (92.0)	3.00 (2.87, 3.13)	155.58 (1)	< 0.001
Non-de-escalation	262	243 (92.7)	5.00 (4.96, 5.04)		

[a] *Kaplan-Meier analysis*

escalation group ($p < 0.001$).

The analysis of all-cause mortality within 28 days of life for both groups is summarized in Figure 3. Statistically, the results showed no significant difference in the 28-day mortality between groups ($p = 0.052$). Further post-hoc power analysis showed only 37.4% of study power for all-cause mortality.

The details of the cost analysis are shown in Figure 4. The significant difference in costs between both groups was noted from day 2 of treatment onwards ($p < 0.001$). The ICER of non-de-escalation compared to the de-escalation group was RM 197.55 (USD 47.80) per time saved. This result indicated that non-de-escalation costed an additional USD 47.80 for each additional day needed to cure.

Discussion

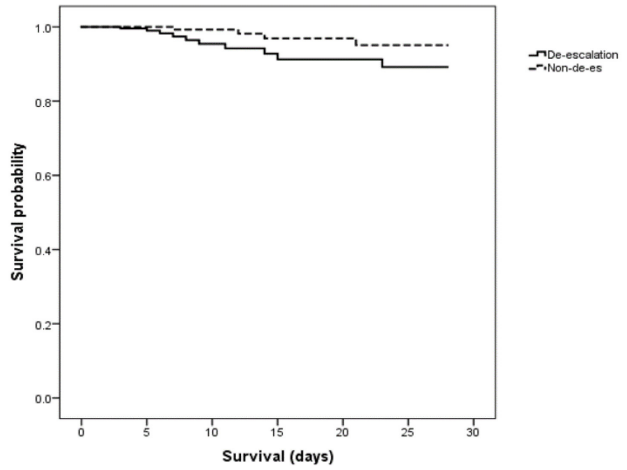
Local and international guidelines for the management of EONS strongly recommend early de-escalation of empirical antibiotics, within 72 hours of treatment [19,28,29]. However, each newborn must be evaluated clinically if the blood culture result was sterile. This study found that the newborns in the non-de-escalation group generally had a significantly greater number of risks and symptoms of sepsis compared to the de-escalation group. The de-escalation practice should not occur if newborns showed clear risks or signs of sepsis [12].

Cesarean delivery; lack of antenatal care; and poor appearance, pulse, grimace, activity, respiration (APGAR) score at the 1st and 5th minutes were significantly higher in the de-escalation group, compared to the non-de-escalation group. Cesarean delivery has been linked to a reduced risk of EONS compared to normal vaginal delivery [30]. An incomplete history of maternal complications may complicate an early diagnosis of sepsis and lead to a short treatment duration with empirical antibiotics for EONS due to the unreported risk of maternal complications [31]. Although low APGAR scores at birth can cause the immune system to be low and increase the risk of sepsis [32,33], the results of this study indicated that low APGAR scores did not prevent physicians from an early de-escalation of empiric antibiotics for EONS if newborns were clinically well.

The results of this study also showed that, where the majority began treatment within 24 hours of birth with a penicillin and gentamicin combination, there was no significant difference in the time of first dose administration of empiric antibiotics for both groups. This is a good practice for both groups, as immediate treatment has been proven to provide optimal treatment for suspected EONS [34].

A comparison of treatment outcomes up to 7 days of life showed no significant difference in treatment failure between the two groups, with the non-de-escalation group having a shorter treatment duration. Further association between shorter treatment duration

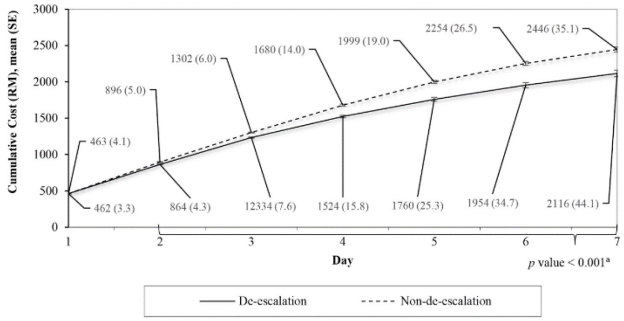
Figure 3. All-cause mortality in 28-days of life between de-escalation and non-de-escalation groups (N = 524).



Variables	n	Mortality, n (%)	Mean (95% CI) (days)	Log Rank[a] (df)	*p* value[a]
De-escalation	262	10 (3.8)	26.32 (25.30, 27.34)	3.766 (1)	0.052
Non-de-escalation	262	4 (1.5)	27.36 (26.75, 27.98)		

[a] *Kaplan-Meier analysis*

Figure 4. Cost analysis between de-escalation and non-de-escalation groups in 7 days.



Practice	Data		ICER		
	Cost/ newborn (RM)	Time to optimal/ newborn (day)	Cost (C)	**Time saved (E)	C/E ratio (cost per time saved)
Non-de-escalation	2,380.63	4.71			
De-escalation	2,042.82	3.00	337.81	1.71	197.55

[a] Mann Whitney U-test; SE: standard error. RM: Ringgit Malaysia; ICER: incremental cost-effectiveness ratio (ICER); C: cost per newborn; ** time saved to optimal therapy per newborns (E). A total of 241 de-escalation and 243 non-de-escalation newborns were treated successfully.

with hospital discharge or length of stay and overall clinical recovery was difficult to conclude due to multiple factors involved, especially in premature patients. Besides, the de-escalation group showed higher mortality even though it did not reach statistical significance, probably due to the higher number of cases with poor antenatal care, a poor APGAR score at 1 and 5 minutes, and sepsis relapse incidence in this group. However, the results are in line with previous research whereby the short duration of empirical antibiotics in EONS did not increase the risk of treatment failure defined as sepsis relapse within 2 weeks [17] and did not increase the risk of sepsis-related mortality [16].

Cost analysis showed that the de-escalation group had a significantly lower total cumulative cost starting from day 2 of treatment and the ICER indicated additional cost needed for the non-de-escalation group to reach optimum therapy each day. By using the ICER indicator, the de-escalation strategy was proven to be more cost-effective, and these savings could change in different hospital facilities with varying cost structures. However, a recent systematic review and meta-analysis evaluating the impact of antibiotic de-escalation showed inconclusive cost impact due to limited studies reported on cost analysis [35]. Even though there is limited evidence on cost-effectiveness, early de-escalation potentially reduced antibiotic resistance and overall healthcare resource utilization [36].

The limitations of this study include analysis based on prospective observation of actual practice. This study holds value, particularly in newborn contexts where randomization is impractical and unethical. This study allows researchers to gather insights into real-world practices and potential effects of early antibiotic de-escalation in newborns with suspected EONS even though they cannot definitively establish causation like randomized controlled trials (RCTs). However, the findings may improve if it is conducted under controlled conditions.

Besides, this study was underpowered to detect the all-cause mortality differences between the comparison groups and required at least 700 subjects per arm to reach more than 75% study power. However, even when the number of subjects increases, there is no guarantee that the mortality detection will be improved because, in fact, the younger children have more robust immune systems and fewer co-morbidities; hence, the risk of mortality is generally low [37].

Finally, there were potential biases that could have influenced antibiotic de-escalation decisions, such as variations in clinical experience or local hospital policy. Future studies should focus on specific areas, including investigating the impact of de-escalation in different subgroups, such as premature babies or those with underlying health issues.

Acknowledgements

We (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 Hospital Sungai Buloh; and Dr Rashidah Mohd Zaini, Head of Pediatric Department Hospital Shah Alam; for their support toward this research project. We are also thankful to the Faculty of Pharmacy Universiti Kebangsaan Malaysia; Pharmacy Department and Neonatal Intensive Care Unit of Sungai Buloh Hospital; Hospital Shah Alam; and Hospital Canselor Tuanku Muhriz for their technical support.

Corresponding author

Dr Nazedah Ain Ibrahim, RPh. PhD.
Pharmacy Department, Hospital Tunku Azizah,
Lot 25, Jalan Raja Muda Abdul Aziz, 50300, Kuala Lumpur, Malaysia.
Tel: 03-26003000, ext: 1236
Email: nazedah@moh.gov.my

Conflict of interests

No conflict of interests is declared.

References

1. Willis Z, Maurice A de S (2019) Strategies to improve antibiotic use in the neonatal ICU. Curr Opin Pediatr 31: 127–134. doi: 10.1097/MOP.0000000000000716.
2. Akrami K, Sweeney DA, Malhotra A (2016) Antibiotic stewardship in the intensive care unit: tools for de-escalation from the American Thoracic Society Meeting 2016. J Thorac Dis 8: S533–S535. doi: 10.21037/jtd.2016.07.28.
3. Klingenberg C, Kornelisse RF, Buonocore G, Maier RF, Stocker M (2018) Culture-negative early-onset neonatal sepsis — at the crossroad between efficient sepsis care and antimicrobial stewardship. Front Pediatr 6: 285. doi: 10.3389/fped.2018.00285.
4. Paolucci M, Landini MP, Sambri V (2012) How can the microbiologist help in diagnosing neonatal sepsis? Int J Pediatr 2012: 14. doi: 10.1155/2012/120139.
5. Liu P, Ohl C, Johnson J, Johnson J, Williamson J, Beardsley J, Luther V (2016) Frequency of empiric antibiotic de-escalation in an acute care hospital with an established antimicrobial stewardship program. BMC Infect Dis 16: 751. doi: 10.1186/s12879-016-2080-3.
6. Camargo LFA (2013). The "de-escalation concept" and antibiotic de-escalation: a missed opportunity? Shock 39: 29–31. doi: 10.1097/SHK.0b013e31828faf02.
7. Singh S, Menon VP, Mohamed ZU, Mohamed ZU, Anil Kumar V, Nampoothiri V, Sudhir S, Moni M, Dipu TS, Dutt A, Edathadathil F, Keerthivasan G, Kaye KS, Patel PK (2018) Implementation and impact of an antimicrobial stewardship program at a tertiary care center in South India. Open Forum Infect Dis 6: ofy290. doi: 10.1093/ofid/ofy290.

8. Tabah A, Cotta MO, Garnacho-Montero J, Schouten J, Roberts JA, Lipman J, Tacey M, Timsit JF, Leone M, Zahar JR, De Waele JJ (2016) A systematic review of the definitions, determinants, and clinical outcomes of antimicrobial de-escalation in the intensive care unit. Clin Infect Dis 62: 1009–1017. doi: 10.1093/cid/civ1199.
9. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Land GA, Peterson LE, Musser JM (2013) Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. Arch Pathol Lab Med 137: 1247–1254. doi: 10.5858/arpa.2012-0651-OA.
10. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit a proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 162: 505–511. doi: 10.1164/ajrccm.162.2.9909095.
11. Álvarez-lerma F, Alvarez B, Luque P, Ruiz F, Quintana E, Sanz-rodriguez C, Group S (2006) Empiric broad-spectrum antibiotic therapy of nosocomial pneumonia in the intensive care unit: a prospective observational study. Crit Care 10: R78. doi: 10.1186/cc4919.
12. Knaak E, Cavalieri SJ, Elsasser GN, Preheim LC, Gonitzke A, Destache CJ (2013) Does antibiotic de-escalation for nosocomial pneumonia impact intensive care unit length of stay? Infect Dis Clin Pract 21: 172–176. doi: 10.1097/IPC.0b013e318279ee87.
13. Khan RA, Aziz Z (2017) A retrospective study of antibiotic de-escalation in patients with ventilator-associated pneumonia in Malaysia. Int J Clin Pharm 39: 906–912. doi: 10.1007/s11096-017-0499-2.
14. Montravers P, Augustin P, Grall N, Desmard M, Allou N, Marmuse J, Guglielminotti J (2016). Characteristics and outcomes of anti-infective de-escalation during health care-associated intra-abdominal infections. Crit Care 20: 83. doi: 10.1186/s13054-016-1267-8.
15. Viasus D, Simonetti AF, Garcia-Vidal C, Niubó J, Dorca J, Carratalà J (2017) Impact of antibiotic de-escalation on clinical outcomes in community-acquired pneumococcal pneumonia. J Antimicrob Chemother 72: 547–553. doi: 10.1093/jac/dkw441.
16. Leandro C, Ayers LW (2003) Duration of empiric antibiotics for suspected early onset sepsis in extremely low birth weight infants. Infect Control Hosp Epidemiol 24: 662–666. doi: 10.1086/502270.
17. Pasha YZ, Ahmadpour-Kacho M, Behmadi R, Jahangir T (2014) 3-day versus 5-day course of intravenous antibiotics for suspected early onset neonatal sepsis: a randomized controlled trial. Iran J Pediatr 24: 673–678.
18. Garnacho-montero J, Escoresca-ortega A (2015) Antibiotic de-escalation in the ICU: how is it best done? Curr Opin Infect Dis 28: 193–198. doi: 10.1097/QCO.0000000000000141.
19. Muhammad Ismail HI, Mohd Ibrahim H, Ng HP and Thomas T (2018) Paediatric Protocols, 4th edition. Malaysia: Ministry of Health Malaysia. 114–116.
20. Masterton RG (2011) Antibiotic de-escalation. Crit Care Clin 27: 149–162. doi: 10.1016/j.ccc.2010.09.009.
21. Chong E, Reynolds J, Shaw J, Forur L, Delmore P, Uner H, Bloom BT, Gordon P (2013) Results of a two-center, before and after study of piperacillin - tazobactam versus ampicillin and gentamicin as empiric therapy for suspected sepsis at birth in neonates </= 1500 g. J Perinatol 33: 529–532. doi: 10.1038/jp.2012.169.
22. Lugt NM Van Der, Smits-wintjens VEHJ, Zwieten PHT, Van, Walther FJ (2010) Short- and long-term outcome of neonatal hyperglycemia in very preterm infants: a retrospective follow-up study. BMC Pediatr 10: 52. doi: 10.1186/1471-2431-10-52.
23. Kostelanetz AS (2004) Survival of the very-low-birth-weight infants after cardiopulmonary resuscitation in neonatal intensive care unit. J Perinatol 24: 279–283. doi: 10.1038/sj.jp.7211054.
24. Gutbrod T, Wolke D, Soehne B Ohrt B, Riegel K (2000) Effects of gestation and birth weight on the growth and development of very low birthweight small for gestational age infants: a matched group comparison. Arch Dis Child Fetal Neonatal Ed 82: F208–F214. doi: 10.1136/fn.82.3.F208.
25. Suruhanjaya Perkhidmatan Awam Malaysia (2020) Minimum-maximum salary schedule for management and professional groups. Available: www.spa.gov.my link. Accessed: 21 January 2020. [Article in Malay].
26. Metsvaht T, Pisarev H, Ilmoja M, Parm Ü, Maipuu L, Merila M, Müürsepp P, Lutsar I (2009) Clinical parameters predicting failure of empirical antibacterial therapy in early onset neonatal sepsis, identified by classification and regression tree analysis. BMC Pediatr 9: 72. doi: 10.1186/1471-2431-9-72.
27. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ and Stoddart GL (2005) Methods for the economic evaluation of health care programmes. 3rd edition. New York: Oxford University Press. 103–136. doi: 10.1093/oso/9780198529446.001.0001.
28. National Institute for Health and Care Excellence Guideline (2012) Neonatal infection (early onset): antibiotics for prevention and treatment. Available: https://www.nice.org.uk/guidance/ng195. Accessed: 21 January 2020.
29. Polin RA (2012) Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics 129: 1006–1015. doi: 10.1542/peds.2012-0541.
30. Signore C, Klebanoff M (2008) Neonatal morbidity and mortality after elective cesarean delivery. Clin Perinatol 35: 361–371. doi: 10.1016/j.clp.2008.03.009.
31. Shane AL, Sánchez PJ, Stoll BJ (2017) Neonatal sepsis. Lancet 390: 1770–1780. doi: 10.1016/S0140-6736(17)31002-4.
32. Gebremedhin D, Berhe H, Gebrekirstos K (2016) Risk factors for neonatal sepsis in public hospitals of Mekelle City, North Ethiopia, 2015: unmatched case control study. PLoS One 11: e0154798. doi: 10.1371/journal.pone.0154798.
33. Hayun M, Alasiry E, Daud D, Febriani DB, Madjid D (2015) The risk factors of early onset neonatal sepsis. Am J Clin Exp Med 3: 78–82. doi: 10.11648/j.ajcem.20150303.11.
34. Cotten CM (2016) Adverse consequences of neonatal antibiotic exposure. Curr Opin Pediatr 28: 141–149. doi: 10.1097/MOP.0000000000000338.
35. Alanazi A, Almuhaya R, Almohaimeed M, Alahmari N, Abdulrahim N, Basyouni M, Althikrallah F, Al Badwyi J, Khallaf A, Albalawi K, Almalki A, Alsaedi K, Bakarman F, Alotaibi F and Mohammed Kanan (2023) Impact of antibiotic de-escalation on antibiotic consumption, length of hospitalization, mortality, and cost: a systematic review and meta-analysis. Pharmacoepidemiology 2: 289–306. doi: 10.3390/pharma2040025.
36. Teshome BF, Park T, Arackal J, Hampton N, Kollef MH, Micek ST (2024) Preventing new Gram-negative resistance through beta-lactam de-escalation in hospitalized patients with sepsis: a retrospective cohort study. Clin Infect Dis 79: 826–833. doi: 10.1093/cid/ciae253.
37. Fay MJ, Bryant PA (2020) Antimicrobial stewardship in children: where to from here? J Paediatr Child H 56: 1504–1507. doi: 10.1111/jpc.15209.

Annex – Supplementary Items

Supplementary Table 1. Medical charges.

Item	Cost in RM	Source / reference
NICU charge per day	300.00	Fees (Medical) Act
Staff minimum salary per day per 5 newborns		
Doctor grade UD48	34.74	[25]
Nurse grade U29	11.98	[25]
Antibiotic per unit		Pharmacy logistic office
Gentamycin 80 mg	0.55	
Benzylpenicillin 1 mg	2.32	
Ampicillin 500 mg	2.32	
Amikacin 250 mg	2.90	
Cefotaxime 500 mg	4.06	
Meropenem 500 mg	9.90	
Laboratory charges per test		Fees (Medical) Act
Blood culture (pediatric)	40.00	
Complete blood count (CBC)	40.00	
Urea and electrolyte	38.00	
Creatinine	35.00	
C-reactive protein (CRP)	60.00	
Aminoglycoside therapeutic drug monitoring (TDM)	30.00	

NICU: neonatal intensive care unit; RM: Ringgit Malaysia.