

A REVIEW OF ANTIBIOTIC USED IN SUSPECTED EARLY-ONSET NEONATAL SEPSIS FROM MALAYSIAN PERSPECTIVE: WHICH ONES TO CHOOSE AND HOW LONG TO GIVE?

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ABSTRACT

Objective: Suspected early-onset sepsis is a common diagnosis among neonates which warrants admission to the neonatal intensive care unit. Prolonged empiric antibiotic is the biggest concern and treatment duration is still controversial. Antimicrobial stewardship (AMS) program promotes early antibiotic de-escalation to reduce unnecessary antibiotic exposure and its implementation in the intensive care setting seems to be feasible. The primary objective of this review was to compare the existing guidelines and review the literature regarding choice and duration of empiric antibiotic in managing suspected early-onset neonatal sepsis.

Methods: Two Malaysian Ministry of Health guidelines were compared with guidelines from America (n=1), Australia (n=1), and United Kingdom (n=2). The literature search was conducted from January to June 2017 through open access journal and databases available at the author's institution library (EBSCOHost, Ovid and Science Direct).

Results: All guidelines recommended similar antibiotics range and suggested to review treatment at 36–72 h post antibiotic exposure. A total of 113 abstracts and full articles were identified, and only 11 full-text articles published in English were related to the subject of interest. All studies show differences either in study design, choice of antibiotics, treatment duration or outcome measures; thus, a meta-analysis was not possible to be conducted.

Conclusion: From this review, we found the potential to perform early empiric antibiotic de-escalation especially in clinically well-appearing neonates, and it is best to customize our guidelines based on local evidence which justifies the need for more local research in this area.

Keywords: Neonate, Early onset sepsis, Guideline, Treatment, Duration.

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INTRODUCTION

World Health Organization estimated that 6.9 million possible serious bacterial infections among neonates occurred in South Asia, Sub-Saharan Africa, and Latin America in 2012 [1]. Neonatal sepsis is the third common cause of neonatal death [1]. In Malaysia, neonatal deaths for the year 2000 were reported at 1 per 2000 deaths [2]. Infection remains a significant contributing factor for mortality and morbidity in view of their immature immune system especially in premature neonates [3,4].

Early onset sepsis (EOS) is defined as sepsis occurring within 72 h of life [5] and caused by vertical transmission from mother to infant before delivery or during the delivery process [6-8]. Maternal infection during pregnancy commonly presented with chorioamnionitis and prevalence of neonates confirmed EOS was around 17.2% in mother confirm chorioamnionitis infection [9-11]. It is recommended in the guidelines to start the neonates with an empiric antibiotic if the mother diagnoses with chorioamnionitis which leads to overuse of antibiotic [12]. There is ongoing debating on how long to keep the antibiotic if the baby remains well [12].

From the global perspective, common microorganism related to EOS is Group B *Streptococcus* (GBS) [13,14]. However, after the wide exposure to intrapartum antibiotic prophylaxis (IAP) in mothers with GBS during pregnancy, the paradigm was shifted from prominently Gram-positive to Gram-negative organisms, especially *Escherichia coli* [15-17]. Ongoing microorganism culture and sensitivity surveillance are recommended to guide the choice of empiric antibiotics [18]. A recent local study reported that 77% from 22 proven EOS cases grew Gram-positive organism mainly coagulase-negative staphylococci despite the IAP exposure and similar finding was reported elsewhere [19,20].

The role of empiric antibiotic in suspected EOS is crucial to reduce the morbidity and mortality risks [21-23]. This is a biggest challenge to the physician since signs and symptoms of neonatal sepsis are nonspecific and empiric antibiotic often used in neonates who are not infected [4,7,24]. It is pertinent that the choice of empiric antibiotic in suspected EOS must have both Gram-positive and Gram-negative bacterial coverage. The choice of antibiotic must be driven by guideline based on common microorganism in maternal genitourinary tract and their susceptibility patterns [25]. The combination of penicillin plus gentamicin, ampicillin plus gentamicin, and ampicillin plus cefotaxime is the most common combinations therapy used for empiric treatment in suspected EOS and listed as top 10 most common drugs utilization in neonatal intensive care unit (NICU) [4,25-28]. In some studies, they also reported the use of amikacin combinations in the management of suspected EOS [29,30].

A Cochrane review on antibiotic regimes for suspected EOS by Mtitimila and Cooke 2004 identified only two randomized control trials (RCTs) comparing effectiveness of timentin versus piperacillin plus gentamicin and ceftazidime versus gentamicin plus benzylpenicillin. Both studies showed no significant difference in primary outcome, mortality in 28 days and treatment failure defined as the need to change empirical antibiotic therapy. Nonetheless, both studies were from the 80's and some of the antibiotics were no longer used at present; thus, findings from these studies were irrelevant to current practice [6]. The reviewer suggested to conduct more RCTs to conclude which antibiotic regimen is favorable. Thus, a review of more recent RCTs involving this topic is vital in providing more information regarding any antibiotic regimen used in the management of suspected EOS.

The duration of empirically initiated antibiotic is controversial when blood culture is sterile and clinical signs and symptoms resolve

rapidly [30]. Cotton and Smith *et al.* reported that through early initiation of empiric antibiotic could potentially save lives; however, there were limited data on treatment duration [31]. They also suggested that a lack of universal approach to interpreted infection biomarker in the critical phase of neonatal sepsis was the contributing factor for prolonged empiric antibiotic use [31,32]. Thus, proper guidelines are important to minimize both the overused and prolonged use of antibiotic as well as decrease the risks of resistance [33].

In recent years, Antimicrobial stewardship (AMS) programs have been promoted widely in Malaysia [34]. The purpose of this program is to ensure the appropriateness in the choice and administration of antibiotics. This program involves multidisciplinary team approach which includes doctors, pharmacists, microbiologists, and infection control. AMS role is to limit inappropriate antibiotic used and prevent multiresistant organism [35]. Besides, AMS also aim to improve patient outcomes and reduce health-care cost without compromising the quality of care [34,36]. However, AMS in NICU is not widely implemented in Malaysia due to limited expertise in pediatric infectious disease; nevertheless, the concept can be adopted.

Early antibiotic de-escalation is one of the approaches used by the AMS team to reduce the antibiotic misuse [37]. Antibiotic de-escalation ideally should not be protocolized but need to be performed by the doctor in charge of the patients in accordance with the clinical findings and organism identified from culture and sensitivity tests [38]. It is defined as a reduction of antibiotic spectrum by either reducing the number of antibiotics, stepping down to narrower spectrum or discontinuation of all antibiotics if there is no obvious infection [39-41]. Antibiotic de-escalation was feasible to be implemented in critical care patients with pneumonia, intra-abdominal infection and septic shock without increasing mortality risk [40,42-46].

The appearance of a clinical pharmacist in NICU has been developed tremendously with the important role to ensure pharmacotherapy optimization, appropriateness, and safety [47]. The physician's acceptance toward pharmacist intervention in NICU was reported high especially in the appropriateness of drug dose and frequency [48]. Hence, the presence of a clinical pharmacist in NICU can be fully utilized by working together with a physician to ensure appropriateness of empiric antibiotics choice and duration and helping the de-escalation process in suspected EOS.

The purpose of this review is to compare Malaysian guidelines with other established guidelines and conduct a review on recent supporting evidence from published articles on empiric antibiotic choice and treatment duration in suspected early-onset neonatal sepsis.

METHODS

Established guidelines available online were compared with local published guidelines. Choice of treatment and duration recommended by guidelines was extracted and presented in a comparison table.

A literature search to identify published articles related to the management of suspected EOS was done from June to December 2017. In this review, we included all types of study design that described antibiotics choice and treatment duration used in EOS. The searched structure involved using Boolean operators for a combination of following terms: EOS, neonatal, treatment, duration, guideline, and management.

The search was limited to publication from the year 2000 and above. The list of title and abstract from open access journal and local university electronic databases (EBSCOHost, Ovid and Science Direct) was screened, and duplications were removed. Full-text articles written in English and defined EOS as suspicion of neonatal sepsis within 3 days after birth regardless of the gestational age were retrieved and included in the review.

Quality of evidence was assessed using Cochrane Risk of Bias tool and Newcastle-Ottawa Quality Assessment Scale. The information regarding empiric antibiotic regimens, treatment duration, and treatment outcome were then extracted from articles and compared in a structured table. The review process involved two independent reviewers.

RESULTS

Guidelines comparison

Two local guidelines by the Ministry of Health Malaysia (MOH), namely 3rd Pediatric Protocol [49] and 2nd National Antibiotic Guideline (NAG) (2014) [50] were reviewed. Treatment for suspected early-onset neonatal sepsis and duration to review was extracted and documented in Table 1. Four other guidelines from Australia (n=1), United State of America (n=1), and United Kingdom (UK) (n=2) were identified and compared.

The first line empiric antibiotic treatment suggested in local guideline was intravenous (IV) C-penicillin or ampicillin in combination with gentamicin which is in concordance with the Australian guideline [51]. The American guideline [30] suggested the use of IV ampicillin in combination with aminoglycosides or third-generation cephalosporin as an alternative to aminoglycosides whereas UK guidelines [52,53] suggested IV C-penicillin in combination with Gentamicin. IV cefotaxime stated as an alternative treatment in most guidelines to cover meningitis due to its excellent cerebrospinal fluid penetration properties [30,50-53].

Table 1: Guidelines comparison on choice of antibiotic for EOS

Guideline	Treatment	Duration
Local guideline 3 rd Pediatric Protocol MOH [49]	IV C-penicillin or ampicillin plus gentamicin	Trace culture results after 48-72 h. Adjust antibiotics according to the results
2 nd NAG MOH	IV C-penicillin or ampicillin plus gentamicin or ampicillin plus cefotaxime (alternative)	Review at 36 h with culture result
International guideline South Australian perinatal practice guideline [51] (AAP) [30]	IV C-penicillin or ampicillin plus gentamicin IV ampicillin plus aminoglycoside (usual gentamicin as synergy) or IV ampicillin plus 3 rd generation cephalosporin (Cefotaxime)	Duration of treatment depends on clinical circumstances but is at least 48 h Empiric antibiotic duration remains controversial. Suggest to off at 48 h if the probability of sepsis is low
NICE UK[52] and NHS UK [53]	IV C-penicillin plus gentamicin	Consider stopping antibiotics 36 h after starting antibiotics if blood culture is negative, and initial suspicion of infection was not strong

AAP: American academy of pediatrics, MOH: Ministry of Health, UK: United Kingdom, NAG: National Antibiotic Guideline, NICE: National Institute for Health and Care Excellence, NSH: National Health Service, IV: Intravenous, EOS: Early-onset sepsis

Duration to review the empiric antibiotic treatment varied between guidelines. Only 3rd Pediatric Protocol [49] stated to review treatment 48–72 h whereas Australian and American of Pediatrics (AAP) guidelines recommend reviewing at 48 h. Both UK guidelines (NICE and NHS) suggested reviewing treatment as early as 36 h postempiric antibiotic exposure in concordance with the Malaysian NAG [50,52,53].

All guidelines suggest for blood culture to be taken before empiric antibiotic administration and treatment duration should be reviewed with the presence of blood culture result [30,50-53]. NICE guideline specifically recommends measuring C-reactive protein (CRP) concentration at sepsis presentation and to repeat measurement 18–24 h after the presentation to guide the treatment duration [52].

The AAP guideline suggests discontinuing antibiotic at 48 h if sepsis probability is low [30]. Whereas NICE recommends stopping therapy at 36 h if blood culture is negative, initial clinical suspicion of infection was not strong, baby's clinical condition is reassuring with no clinical indicators of possible infection, and the trends of CRP concentration are reassuring [52].

Evidence-based compilation

The summary of the review process is shown in Fig. 1. A total of 113 articles identified using searched keywords; suspected EOS, neonatal, treatment, duration, guideline, and management from open access journal and databases. After the title screening and article assessment, only 11 articles met the selection criteria and 102 were excluded from further assessment.

The review finding from 11 articles is summarized in Table 2. All articles were published between the year 2003 and 2016 with three RCTs, two prospective, and six retrospective studies. The largest sample population was 128,914 babies reported in a retrospective study by Clark *et al.* [25] and the smallest sample population was 59 babies reported in a RCT study by Tewari and Jain [54].

Out of 11 articles, seven were Caucasian populations, three Asian, and one African. Three studies used full-term or near-term neonates' population and 4 studies used premature or low birth weight neonate's population in their research. Remaining 4 studies reported their results in the form of gestational age range or comparison between full-term and premature neonates' group. Meta-analysis was not possible in view of wide variations of study design and differences in population characteristics and study endpoints measured.

Choice of empiric antibiotic regime

Eleventh articles clearly stated the choice of antibiotics used in their study. Only 6 articles compared endpoint of two different treatments. Four studies compared two different treatment combinations (ampicillin plus gentamicin vs. piperacillin-tazobactam; ampicillin plus gentamicin

versus C-penicillin plus gentamicin; ampicillin plus cefotaxime versus ampicillin plus gentamicin; and ampicillin plus aminoglycosides versus C-penicillin plus aminoglycosides) [21,25,26,55]. One study compared two different monotherapies (amikacin vs. piperacillin-tazobactam) [54].

Two studies compared ampicillin plus gentamicin and penicillin plus gentamicin regime; one RCT and one prospective study [21,26]. The outcome of both studies showed no significant difference in mortality endpoint between regimes [21-26]. The RCT study also reported that treatment failure defined as antibiotic escalation within 72 h and mortality in 7 days of life was no differences between both regimes [26].

Prolonged postnatal exposure to an empiric antibiotic is a risk factor for developing necrotizing enterocolitis (NEC) [57,61]. Piperacillin-tazobactam showed less NEC and diaper rash effect as compared to ampicillin plus gentamicin [55] and similar efficacy with amikacin monotherapy [54] in neonates at risk of EOS.

One retrospective study comparing ampicillin plus or gentamicin regimes showed that concurrent use of cefotaxime was an independent factor associated with increased risk of neonatal death [25]. In addition, prolonged or extensive use of third-generation cephalosporin has been identified as a risk for invasive candidiasis. Routine use of cefotaxime for treatment of EOS had led to reports on rapid development of resistance [30].

From the review, we found that first-line empiric antibiotic regime suggested in the guidelines (ampicillin plus gentamicin or penicillin plus gentamicin) seems to be favorable with similar effectiveness. Piperacillin-tazobactam has the potential to be an alternative treatment in the management of suspected early-onset neonatal sepsis [54,55]. The use of cefotaxime antibiotic, however, should be limited due to undesirable outcome [62].

Treatment duration with antibiotics for EOS

Nine studies reported the treatment duration in mean (standard deviation) day [58,59], median interquartile range day [21,25,55,60] or day [3,56]. The longest treatment duration for suspected EOS reported in this compilation was ≥ 7 days [3] and the shortest was 3 days or less [3,57]. Two studies did not mention clearly the treatment duration used in their study [26,54].

Three studies compared endpoint of similar treatment combinations (ampicillin plus amikacin, ampicillin plus gentamicin, and ampicillin plus aminoglycosides) with different treatment durations (3-day vs. 5-day; < 5 -day vs. ≥ 5 -day; ≤ 3 -day vs. ≥ 7 -day) [3,56,57]. One study used three antibiotics combination (amoxicillin plus cefotaxime plus amikacin) and compared the outcome based on treatment duration [58]. Other studies described the treatment duration without comparing them [21,25,55,59,60].

Cotten *et al.* proved that prolonged treatment > 5 days was associated with NEC [57]. Both Cordero and Ayers and Labenne *et al.* reported that early discontinuation of empiric antibiotic when blood culture is negative can reduce unnecessary antibiotic exposure without compromising clinical outcome (mortality related to EOS and late-onset sepsis). Thus, it will not increase the risk of infectious relapse and may decrease the incidence of late-onset sepsis [3,58].

Ibrahim *et al.* reported that giving an empiric antibiotic for < 4 days will provide prevention of early-onset neonatal sepsis up to 89–95% [59]. Pasha *et al.* reported that treatment duration of 3 days versus 5 days showed no difference in treatment failure for both duration [56].

In this review, we can conclude that by giving a shorter treatment duration (3 days) the desired outcome will not be compromised. Besides, early discontinuation when blood culture is sterile may reduce empiric antibiotic overuse and cut cost [60].

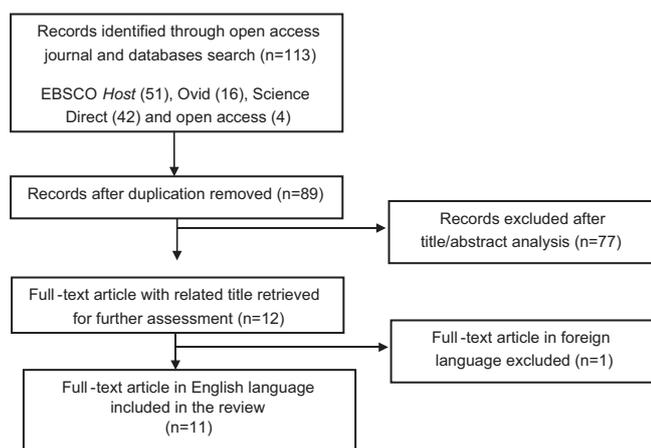


Fig. 1: Flow chart of the article review process

Table 2: Evidence-based compilation

Author and year of publication	Title	Period of data collection	Study design	Population (n); Gestational age (week)	Country, continent	Treatment	Duration (day)	Outcomes and key findings
Comparing the combination of two different antibiotics								
Chong <i>et al.</i> (2013) [55]	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	2007–2009: Ampicillin+gentamicin 2010–2011: Piperacillin-tazobactam	Retrospective cohort two-center	714; Mean (SD) 28 (2.6) versus 28 (2.7)	New Orleans, USA	Ampicillin plus Gentamicin versus Piperacillin-tazobactam	Median: 3	There was no increase in major morbidities however, piperacillin-tazobactam significantly reduced necrotizing enterocolitis and diaper rash incidence
Metsvaht <i>et al.</i> (2009) [26]	Comparison of ampicillin plus gentamicin versus penicillin plus gentamicin in the empiric treatment of neonates at risk of EOS	2006–2007	Open-label cluster-randomized controlled trial two-center	283; Median (IQR) 31 (27–34) versus 31 (28–35)	Estonia, Africa	Ampicillin or C-penicillin plus gentamicin	N/A	Both combinations do not differ in clinical efficacy and have similar influence on the development of gut microflora
Clark <i>et al.</i> (2006) [25]	Empiric use of ampicillin and cefotaxime, compared with ampicillin, and gentamicin, for neonates at risk for sepsis is associated with increased risk of neonatal death	1996–2004	Retrospective cohort	128;914; Median (IQR) 35 (31–38) versus 35 (32–38)	USA	Ampicillin plus cefotaxime or ampicillin plus gentamicin	Median (IQR) Ampi+Cefo: 3 (2–7) Ampi+Genta: 3 (2–6)	Ampicillin plus cefotaxime combinations associated with increased risk of death as compared to ampicillin plus gentamicin
Fjalstad <i>et al.</i> (2016) [21]	Early-onset sepsis and antibiotic exposure in term infants a nationwide population-based study in Norway	2009–2011	Prospective 21 neonatal unit	10,175; Median (IQR) both cohort 40 (38–41)	Norway	Ampicillin or C-penicillin plus Aminoglycosides	Median (IQR) culture-confirmed: 8 (7–10) culture-negative: 6 (5–7)	The incidence of culture-confirmed EOS was in line with previous international reports and the mortality was very low
Comparing two monotherapies								
Tewari and Jain (2014) [54]	Monotherapy with amikacin or piperacillin-tazobactam empirically in neonates at risk for early-onset sepsis: A randomized controlled trial	2009–2011	Randomized controlled trial	59; Range 28-37	India	Amikacin or piperacillin-tazobactam	N/A	Both antibiotics were effective in management of babies with early-onset sepsis

(Contd...)

Table 2: (Continued)

Author and year of publication	Title	Period of data collection	Study design	Population (n); Gestational age (week)	Country, continent	Treatment	Duration (day)	Outcomes and key findings
Comparing two different treatment durations								
Pasha et al. (2014) [56]	3-day versus 5-day course of IV antibiotics for suspected early-onset neonatal sepsis: A randomized controlled trial	2013	Randomized controlled trial Two-center	60; Mean (SD) 37 (1.66) versus 37.2 (2.09)	Mazandaran, Iran	Ampicillin and amikacin	3 and 5-days	No evidence of treatment failure difference in both groups. Treatment failure was defined as reappearance of symptoms of sepsis within two weeks after discontinuation of antibiotics
Cotten et al. (2009) [57]	Prolonged duration of initial empiric antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants	1998–2001	Retrospective cohort 19 centers	4039; Mean (SD) 26.3 (2.01) versus 25.6 (1.89)	North America, USA	Ampicillin Plus gentamicin	Median (IQR): 5 (1-36) versus prolonged: ≥5	Prolonged initial empiric antibiotic therapy may be associated with increased risk of (NEC) or death
Cordero and Ayers (2003) [3]	Duration of empiric antibiotics for suspected early-onset sepsis in extremely low birth weight infants	2000	Retrospective observational	790; Mean (SD) 25 (2) versus 26 (2)	Ohio, USA	Ampicillin plus aminoglycosides	≤3 versus ≥7	Empiric antibiotics discontinuation when blood culture was negative can reduce antimicrobial exposure without compromising clinical outcome
Labenne et al. (2007) [58]	A population-based observational study of restrictive guidelines for antibiotic therapy in early-onset neonatal infections	2002–2003	Prospective observational	1012; Range <35–≥37	Burgundy, France	Amoxicillin plus cefotaxime amikacin therapy	plus Mean (SD) Definite: plus 5.1 (2.3) versus not increased the risk of infectious relapse and may decrease the incidence of (LOS)	Reduced the antibiotic therapy duration does not increase the risk of infectious relapse and may decrease the incidence of (LOS)
Descriptive findings								
Ibrahim et al. (2014) [59]	The effectiveness of empiric antibiotic therapy in the prevention of EOS	2009–2012	Retrospective observational	894; <37 and ≥37	Malaysia	C-penicillin plus gentamicin	Mean (SD) prem <37 week: 4.29 (1.9) term ≥37 weeks: 4.19 (1.76)	The observed prevention of EOS successful rates was between 89% and 95%
Oliver et al. (2016) [60]	Patterns of empiric antibiotic administration for presumed early-onset neonatal sepsis in NICU in the United States	2006–2013	Retrospective cohort	118,624; Range ≥24–≥37	Ohio, USA	Ampicillin plus gentamicin	Mean (SD): 5.3 (1.4)	Variation in antibiotic utilization suggests antibiotic overtreatment of infants with culture unconfirmed EOS is common and costly

IQR: Interquartile range, LOS: late-onset sepsis, NICU: Neonatal Intensive Care Unit, EOS: Early onset sepsis, SD: Standard deviation, NEC: Necrotizing enterocolitis

DISCUSSION

Neonates are a vulnerable population and prone to infections. Suspected early-onset infection is the most common diagnosis in NICU, and the empiric antibiotic is crucial at this point [5]. RCT in the neonatal population is limited due to ethical reasons [6]. Hence, ongoing microorganism culture and sensitivity patterns surveillance are important to establish local antibiotic guideline [18,63].

Bacterial profile and antimicrobial susceptibility pattern of a unit can guide effective empiric antibiotic choices; however, it may vary from center to center depending on the IAP practice [15]. A recent local data reported that nearly 80% of proven EOS had Gram-positive organism isolated from the blood culture [19] and most showed sensitivity toward the recommended first-line empiric antibiotics, C-penicillin plus gentamicin [59].

Established antibiotic guidelines are important to guide the duration of treatment and subsequently influence treatment decision making. By reviewing the probability of sepsis at 36 h [52] to 48 h [30] postempiric antibiotic exposure, it potentially reduces the treatment duration by early de-escalation.

The probability of sepsis can be guided by pre-antibiotic initiation blood culture, full blood count (FBC), serial CRP, and procalcitonin (PCT) [64-66]. Blood culture and FBC are the most common and standard diagnostic measure for EOS in the most center [67]. Proven EOS with positive blood culture remains low at 3% possibly due to inoculation of only 0.5-1.0 ml of blood and it takes 24-48 h for the result [7,19,68,69]. In addition to the blood culture, FBC which includes white blood cell, platelet, and immature-total neutrophil ratio can be useful to rule out sepsis. However, FBC is less specific as compared to CRP [64].

CRP is a widely used biomarker with high specificity but low sensitivity because it also rises with non-infectious event; hence, it cannot be used alone [65,70]. Serial CRP at 24 h and 48 h can be helpful to assist decision-making whether to continue antibiotic despite sterile blood culture and normal FBC [31,71,72]. PCT biomarker is more specific and sensitive than CRP. PCT: CRP ratio can differentiate proven sepsis more clearly, however, PCT test is rather costly [65,73,74].

Guidelines should also consider the local resources and availability on providing laboratory results within the timeline of 36-48 h [40,73]. In certain places with limited resources, it may be difficult to provide efficient laboratory results [31]. Hence, longer time was needed to review sepsis probability and lead to the prolonged antibiotic used [75]. Recent study suggested the used of cord blood to detect CRP elevation as a potential biomarker tools for EOS diagnosis confirmation may potentially reduce the unnecessary antibiotic exposure [76].

Combination therapy with Gram-positive and Gram-negative antibiotic coverage was recommended by all the guidelines to treat suspected EOS [30,49-52]. One study in Boston discovered the potential of early antibiotic withdrawal in premature neonate once blood culture sterile and recommended as one of the antibiotic stewardship opportunity [68]. Meanwhile, early de-escalation by reducing the number of antibiotics within 72 h generally will reduce the risk of resistance and reduce the cost [39]. It is also safe to be implemented in critical care patients [38,77].

In Malaysia, the common causative EOS infection despite the extensive IAP used was Gram-positive organisms, and similar finding was also reported in other studies [19-20,78]. Hence, early withdrawal of Gram-negative antibiotic coverage (aminoglycoside or cephalosporin) as antibiotic de-escalation strategy can potentially be implemented in clinically well-appearance neonate's while waiting for laboratory result confirmation. Shorten the unnecessary aminoglycosides exposure to the neonate will reduce the risk of renal and ototoxicity whereas limited used of cephalosporin will reduce the risk of resistance and invasive candidiasis [1,30, 75,79,80].

Furthermore, early de-escalation and shorter treatment duration in suspected EOS did not increase the risk of treatment failure, and there is a reduced risk of late-onset sepsis, NEC and mortality as reported by previous studies especially in premature neonates [3,57,58,75]. Empiric antibiotics discontinuation by 48 h of life in well-appearing term neonates with chorioamnionitis mother are strongly suggested in the guideline, and it can reduce the antibiotic exposure proven by a recent study conducted by Grant *et al.* [81,82]. It is suggested to continue reviewing future published evidence and produce a systematic review meta-analysis whenever possible.

CONCLUSION

There were differences in the guidelines and practices in managing suspected early-onset neonatal sepsis. However, the current review does not warrant the conclusion of which antibiotic regimes are superior and what is the ideal empiric antibiotic duration due to lack of high-quality RCT study. The best is to customize our guidelines based on local evidence which justify the need for more local research in this area.

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AUTHORS' CONTRIBUTIONS

All authors have contributed equally for bringing this review article effectively.

CONFLICTS OF INTEREST

We (authors) do not have any conflicts of interest.

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