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RESEARCH ARTICLE

THE EFFECTIVENESS OF EMPIRIC ANTIBIOTIC THERAPY IN THE PREVENTION OF EARLY ONSET SEPSIS

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ABSTRACT

Introduction: Neonatal sepsis currently causes 1.6 million deaths annually in developing countries and it is also the main reason for hospitalization in Neonatal Intensive Care Unit. Early onset sepsis still remains the significant risk factor for mortality and morbidity in neonatal period.
Objectives: To describe the outcome of neonates treated with empiric antibiotic for suspected early onset sepsis (EOS).
Methods: Records of neonatal patients at three Malaysian general hospitals admitted within 72 hours of life and prescribed with empirical antibiotic therapy for suspected EOS were retrospectively reviewed.
Results: A total of 894 cases meet the inclusion criteria and divided into premature (<36 weeks) and term (≥37 weeks) neonates group. More than 80% of neonates had respiratory symptoms during admission. However, there were significant differences in diagnosis among premature and term neonates (p=0.001). 60% of suspected EOS cases were premature neonates (n=531) and they were mainly diagnosed for respiratory distress syndrome, congenital pneumonia and presumed sepsis. Majority were born to mothers exposed to antibiotic and steroid during pregnancy. Many of these mothers also had prolong rupture of membrane > 18 h (p>0.05). Premature neonates required longer hospital stay, higher ventilator support and higher surfactant administration (p<0.05). Term neonates (n=363) were mainly diagnosed with congenital pneumonia, presumed sepsis, meconium aspirate syndrome and hypoxic ischemic encephalopathy. These observation were consistent with the high incidence of meconium stained amniotic fluid, perinatal asphyxia and fit symptoms (p<0.05). Penicillin plus gentamicin regimen was the standard therapy started within 24 h of life and the mean treatment duration being less than 4 days. The observed successful rates for the three hospitals were between 89 - 95%.
Conclusions: Majority of the neonates presented with respiratory symptoms and standard empiric antibiotic regimen prescribed showed good coverage for prevention of EOS.

INTRODUCTION

World Health Organization (WHO) estimated about 3.4 million neonates died yearly during the first week of life and 98% occurred in developing countries. Early neonatal mortality rate is 4 per 1000 birth and WHO reported that Malaysia neonatal death for year 2000 at 1 per 2000 birth (WHO, 2006). The main causes of neonatal death are infections, prematurity and birth asphyxia. Neonatal sepsis currently causes 1.6 million deaths annually in developing countries and it is also the main reason for hospitalization in Neonatal Intensive Care Unit (NICU) (Vergnano *et al.,* 2005). Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic sign and symptoms of infection in the first 4 weeks of life. It also can be defined microbiologically by positive cultures from blood, cerebrospinal fluid or urine specimens. WHO collaborating centre for training and research classified early onset sepsis (EOS) as onset of symptoms occurred before 72 hours of life and Late Onset Sepsis (LOS) as onset of symptoms occurred after 72 hours of life. However, there is variation in EOS definition in the literatures and it may range from 48 hours up to 6 days after delivery (Ann 2011; http://www.newbornwhocc.org/pdf/teaching). EOS is normally caused by microorganisms that colonize in the mother's genitourinary tract. The most common microorganism isolated includes group B *Streptococcus* (GBS), *Escherichia coli*, coagulase-negative *Staphylococcus* (CoNS), *Haemophilus influenzae* and *Listeria monocytogenes* (Ann 2011; Schrag *et al.,* 2006; Bizzarro *et al.,* 2008). EOS manifest frequently as pneumonia presented with respiratory distress and less commonly as septicaemia or meningitis. To make an early diagnosis of neonatal sepsis demand a high suspicious index of clinical manifestations (http://www.newbornwhocc.

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org/pdf/teaching). EOS remains the significant risk factor for mortality and morbidity in full term neonates (Leandro and Leona 2003), extremely preterm neonates (Wolkowiez *et al*., 2009) and low birth weight preterm neonates. (Stoll *et al*., 2004) proved that infection in the neonatal period was associated with poor neurodevelopmental and growth outcomes in early childhood (Stoll *et al*., 2005). However, the lack of strong evidence to determine the best empiric antibiotic regimen to prevent and reduce the complication of EOS. Although a randomize control trial is the gold standard to determine the best treatment option, this is unlikely to be performed in neonatal populations. Due to limited information in Malaysia, the retrospective assessment on current practices will give valuable information for future guidance. Our studies objectives aim to describe the characteristics and to evaluate the effectiveness of empiric antibiotic therapy in prevention of EOS in neonates at Malaysian Government Hospitals.

METHODS

Sample Population and Study Design

Records of 1286 neonates born in three General Hospitals (Hospital Raja Permaisuri Bainun Ipoh (HRPB), Hospital Pulau Pinang (HPP) and Hospital Sultanah Aminah Johor Bahru (HSA)) in year 2009 until 2012 were retrospectively reviewed. Neonates were included in the study on the basis of the following criteria for sample selection: (i) Neonates admitted to neonatal ward within 72 hours of life; (ii) Neonates diagnose with suspected EOS (optional); and (iii) Neonates who started with empiric antibiotic regimen penicillin / ampicillin plus gentamicin or ampicillin / penicillin plus cefotaxime combination within 72 hours of life. Subjects must meet criteria number (i) and (iii) for inclusion in the study. Neonates who: discharge or dead within 72 hours post empiric antibiotics exposure; with severe heart complications; start with other empiric antibiotics regimen; with proven infection such as meningitis, Necrotizing Enterocolitis (NEC), and peritonitis; and with congenital malformations were excluded from study. The data was extracted and documented in designated data collection form.

Study Approval

This study was approved by Clinical Research Centre of the Ministry of Health Malaysia (NMRR-11-975-10283) and Research Ethics Committee Universiti Teknologi MARA (UiTM) (600-RMI (5/1/6/01).

Statistical analysis

The neonates were classified into gestational age (GA) group (GA <37 weeks = premature and GA ≥37 weeks = term) for further analysis. Classification according to GA (Labenne *et al*., 2007, Fullas *et al*., 2011 and Weston *et al*., 2011) was commonly used in previous neonatal study because it can be used to predict organ maturity and pharmacokinetics or pharmacodynamics of the drug. All data were entered on a SPSS for windows version 16 and Microsoft Office Excel 2007. The frequencies, percentages, means and standard deviations of each continuous variable studied was calculated and presented in the form of table. Categorical variables were assessed using Pearson Chi-Square test (χ^2 test) or Fisher's exact test. The 95% Confidence Interval (CI) was set for the test whereby the result is significant if $p \leq 0.05$. After stratifying neonates into GA group, Odd Ratio (OR) of each risk factors, clinical manifestations and treatment failure were calculated by using Mantel-Haenszel method. This method is used to pool data from three hospitals in this study and statistical test of homogeneity (Q) were calculated. The purpose of pooling analysis among hospitals was to reduce biases and increase the power of the study by increasing number of data. After OR with 95% CI was calculated, the forest plot techniques have been applied to illustrate the relative strength of risk factors, clinical manifestations and treatment failure in GA group. Treatment failure were determined by changes within 72 hours post antibiotic exposure due to: No improvement or deteriorating; meningitis or suspicion of meningitis; Necrotizing Enterocolitis (NEC) or suspicion of other abdominal infection; microorganism resistant to antibiotic and death in 7 days of life due to sepsis (Metsvaht *et al.,* 2010). The failure and success (reverse treatment failure) of the treatment were assessed by using Kaplan Maier for comparisons between premature and term group and treatment duration. Multivariate analysis, Cox Proportional Hazard Regression was used to identify factors for treatment failure and prolong treatment duration more than 72 hours.

RESULTS

Demographic characteristics

A total of 1286 neonates record have been reviewed and 894 meet the inclusion criteria. Nearly 60% (531) neonates were classified as premature. Demographic characteristics were shown in Table 1. Male showed higher incidence of suspected EOS in both premature and term group as compared to female. The administration of antenatal steroid and antibiotic during pregnancy to the mother was significantly higher in premature neonates. Besides, there was significantly longer hospital stay for premature neonates and they also required ventilator support either intubated or Continuous Positive Airway Pressure (CPAP) and surfactant.

Diagnosis

There was significant difference in premature and term neonates diagnosis during empiric antibiotic started in all hospitals (Fig. 1).

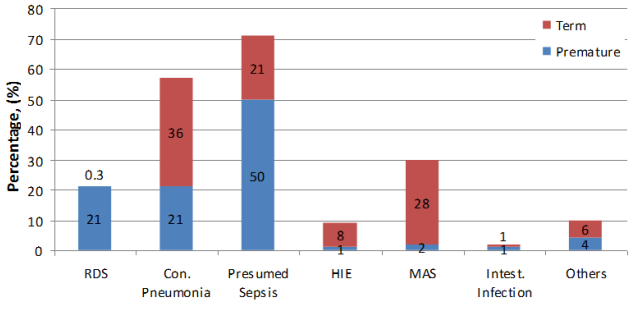

Fig. 1. Diagnosis RDS=Respiratory distress syndrome; Con. Pneumonia=Congenital pneumonia; HIE=Hypoxic ischemic encephalopathy; MAS= Meconium aspirate syndrome; Intest. Infetion= Intestinal infection

Table 1. Demographic characteristics

Characteristics	Premature n= 531	Term n= 363	*p-value*
Birth weight (kg) , mean (±SD)	1.73 (0.56)	3.03 (0.54)	0.001
Gestational age (weeks) , mean (±SD)	32.23 (2.66)	38.89 (1.42)	0.001
Gender, n (%)			0.011
Male	300 (56.50)	242 (66.67)	
Female	231 (43.50)	121 (33.33)	
Ethnicity, n (%)			0.328
Malay	325 (61.20)	233 (64.19)	
Chinese	105 (19.77)	50 (13.77)	
Indian	63 (11.86)	33 (9.09)	
Length of stay (days), mean (±SD)	23.68 (18.52)	8.42 (5.63)	0.001
Antibiotic during pregnancy, n (%)	123 (23.16)	34 (9.37)	0.001
Perinatal steroid, n (%)	216 (64.67)	13 (5.42)	0.001
Ventilator			0.001
Intubated, n (%)	285 (53.67)	191 (52.62)	
CPAP, n (%)	152 (28.62)	57 (15.70)	
Surfactant, n (%)	170 (32.02)	4 (1.10)	0.001

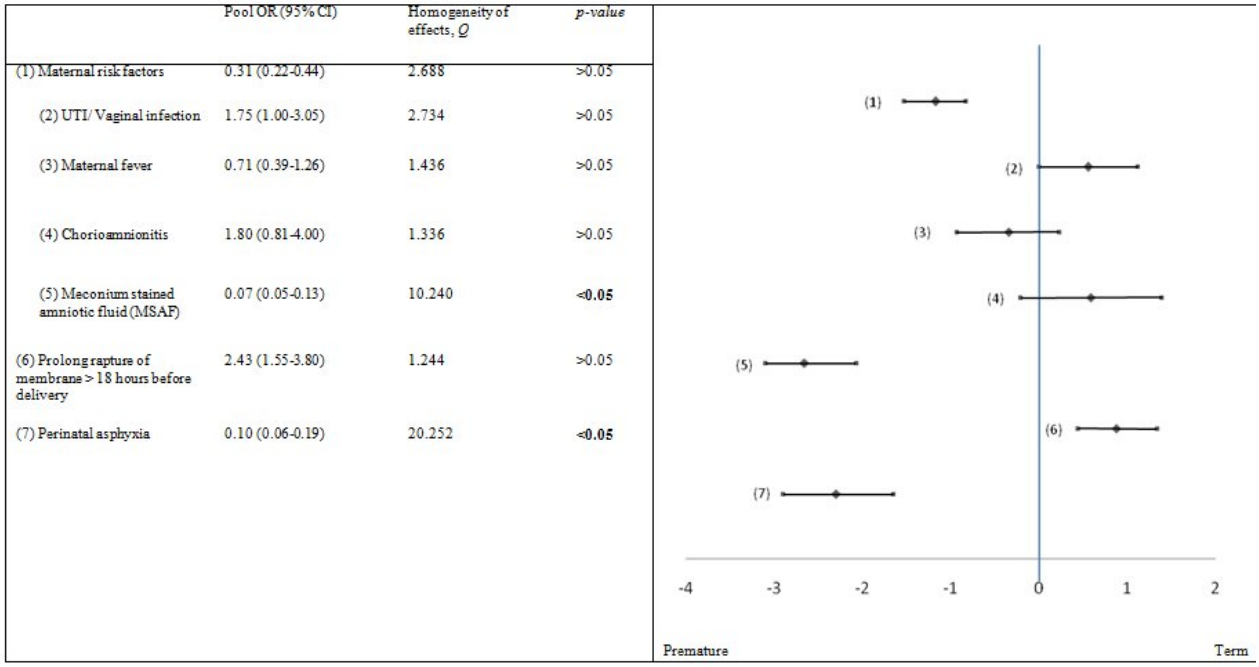

Fig. 2. Forest plot (pool OR) of risk factors. The data are presented as odds ratio (OR) (indicated by diamonds) with the 95% CI (indicated by lines). OR of the term is 0, shift to the left this line indicates lower risk in premature and vice versa. *Q* is referred to the chi-square distribution with 2 degrees of freedom (p >0.05 = homogeneous)

Majority of premature neonates were diagnosed with Respiratory Distress Syndrome (RDS), presumed sepsis and congenital pneumonia. Term neonates were mainly diagnosed with congenital pneumonia, presumed sepsis, Hypoxic Ischemic Encephalopathy (HIE) and Meconium Aspirate Syndrome (MAS).

Risk Factors

Risk factors of suspected EOS are shown in Fig. 2. Overall maternal risk factors showed strong significant difference between groups in all hospitals. The main maternal risk factor that showed differences between groups was Meconium Stained Amniotic Fluid (MSAF) where it occurred more in term neonates. Perinatal asphyxia incidence also showed significantly higher in term neonates. Incidence of prolong rapture of membrane > 18 hours before delivery was significantly higher in premature neonates. However, the statistical test of homogeneity for the three hospitals showed that occurrence of both MSAF and perinatal asphyxia was statistically significant different between hospitals. MSAF incidence occurred less in premature neonates in HSA while overall perinatal asphyxia incidence occurred less in HRPB as compared to the other hospitals.

	Pool OR (95% CI)	Homogeneity of effects, *Q*	*p-value*
(1) Fever	0.38 (0.07-2.25)	4.831	>0.05
(2) Hypothermia	5.04 (0.89-28.49)	0.041	>0.05
(3) Tachycardia	0.60 (0.25-1.43)	5.255	>0.05
(4) Bradycardia	0.60 (0.34-1.08)	3.601	>0.05
(5) Respiratory symptoms	2.15 (1.36-3.40)	13.387	**<0.05**
(6) Apnoea	2.67 (0.98-7.32)	0.119	>0.05
(7) Cyanosis	0.99 (0.67-1.47)	1.019	>0.05
(8) Grunting	0.84 (0.61-1.17)	25.520	**<0.05**
(9) Respiratory distress	9.13 (5.92-14.06)	1.419	>0.05
(10) Tachypnoeic	0.73 (0.53-1.01)	46.430	**<0.05**
(11) Gastrointestinal symptoms	0.73 (0.53-2.05)	1.033	>0.05
(12) Feeding intolerance	1.28 (0.49-3.32)	0.850	>0.05
(13) Vomiting	0.66 (0.26-1.65)	1.320	>0.05
(14) Abdominal distension	1.33 (0.47-3.74)	0.737	>0.05
(15) Fits	0.10 (0.04-0.22)	2.085	>0.05

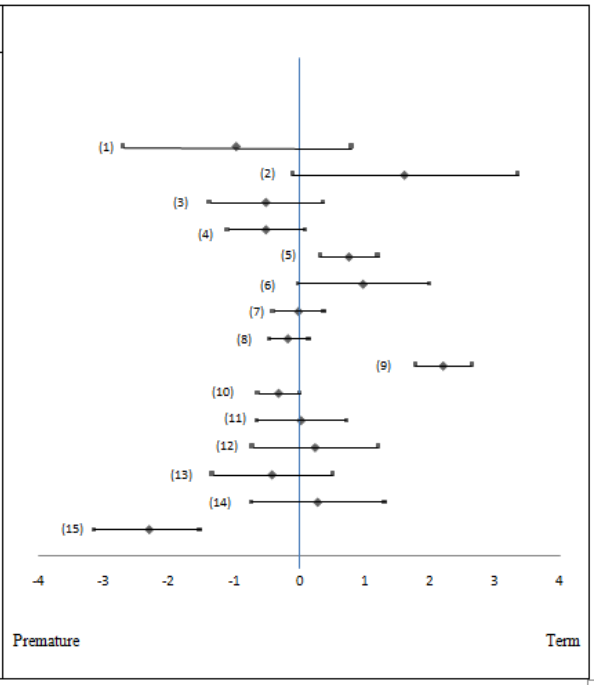

Fig. 3. Forest plot (pool OR) of clinical manifestations. The data are presented as odds ratio (OR) (indicated by diamonds) with the 95% CI (indicated by lines). OR of the term is 0, shift to the left this line indicates lower risk in premature and vice versa. *Q* is referred to the chi-square distribution with 2 degrees of freedom (p >0.05 = homogeneous)

	Pool OR (95% CI)	Homogeneity of effects, *Q*	*p-value*
(1) No improvement / deteriorating	0.86 (0.38-1.98)	5.595	>0.05
(2) Meningitis or suspicion of meningitis	1.08 (0.24-4.85)	3.325	>0.05
(3) NEC or suspicion of other abdominal infection	2.26 (0.55-9.35)	0.340	>0.05
(4) Microorganism resistant to antibiotic	1.59 (0.16-15.58)	0.371	>0.05
(5) Overall treatment failure	1.20 (0.65-2.24)	3.518	>0.05

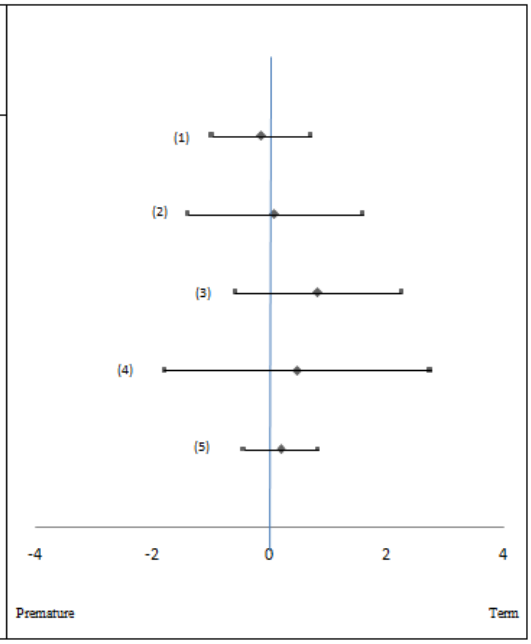

Fig. 4. Forest plot (pool OR) of treatment failure. The data are presented as odds ratio (OR) (indicated by diamonds) with the 95% CI (indicated by lines). OR of the term is 0, shift to the left this line indicates lower risk in premature and vice versa. *Q* is referred to the chi-square distribution with 2 degrees of freedom (p >0.05 = homogeneous)

Clinical Manifestations

The clinical manifestations of neonates at risk of suspected EOS are shown in Fig. 3. More than 80% of neonates at risk of EOS had presented with respiratory symptoms in both GA groups. Overall respiratory symptoms showed significant differences between GA. Respiratory symptoms such as grunting, respiratory distress and tachypnoeic showed significant differences between both groups. More term neonates had grunting and tachypnoeic symptoms than premature neonates. Respiratory distress symptoms were common in premature neonates in all hospitals. There was no

significant difference between both GA groups for thermoregulatory symptoms, cardiac and gastrointestinal symptoms. Fits symptoms occurred significantly higher in term neonates for all hospitals. Statistical test of homogeneity showed overall respiratory symptoms, grunting and tachypnoeic were statistically difference between hospitals.

Empiric antibiotics usage

There was no significant difference in empiric antibiotic regimen used for both GA groups. Penicillin plus gentamicin regimen was the standard therapy in suspected EOS for all hospitals and mostly started within 24 hours of life with mean range of treatment duration of 3 to 4 days (Penicillin dose = 100, 000 ü/kg every 12 hours; Gentamicin dose = 4-5mg/kg every 24-48 hours according to GA). Overall median treatment duration was 3 days in both GA groups. However, there were slight differences in dose and frequency between hospitals. Majority of HRPB neonates with less severity used half dose of penicillin (50,000 ü/kg every 12 hours) compared to other hospitals. HPP used smaller dose and shorter interval to administer gentamicin (2.5-3mg/kg every 24 hours).

Common microorganisms isolated in early onset sepsis

About 84% of total case had culture and sensitivity result traced and documented. 98% of sample sent for culture and sensitivity testing was from blood. Total incidence of proven sepsis was 3.67%. The number of proven sepsis was higher in premature neonates in HPP and HRPB but, it was equal in HSA. Total culture growth showed more gram positive organism compare to gram negative organism in both GA groups. Pattern of microorganism isolated was different between hospitals. HSA isolated more with Bacillus sp.; HPP isolated more with Coagulase Negative Staphylococci (CoNS) while HRPB isolated more with both CoNS and Group B Streptococci (GBS). HRPB isolates had the highest number of gram negative organism compared to other hospitals. HSA showed one incidence of death due to *Streptococcus pneumonia* infection within 7 days of life in term neonate.

Treatment outcome

Half of the cases had completed treatment without changes for both GA groups. Around 27% required changes of antibiotic within 72 hours where 7% classified as treatment failure. The rest required antibiotic changes after 72 hours. There was higher incidence of treatment failure in HSA (11%) but, in other hospitals the incidence of treatment failure was about 5%. Overall treatment failure illustrated in Fig. 4 showed no difference in both GA groups for all hospitals even though treatment failure was higher in HSA premature neonates. Statistical test of homogeneity for all factors of treatment failure show statistical homogeneity between hospitals. Further analysis by using Kaplan Meier on treatment duration showed no significant difference between GA groups (Table 2). Low birth weight (LBW), requirement of CPAP ventilator in 72 hours of life and hypothermia symptom were identified as treatment failure factors as shown in Table 3. There was no significant difference of median treatment duration of treatment success neonates who premature compared to term as shown in Table 4. Multivariate analysis used to determine prolong treatment duration factors and the result showed only fever symptom was correlated with prolong treatment duration (Table 5).

Table 2. Difference of median treatment duration of treatment failure neonates between GA groups

Variables	n	Treatment failure (%)	Median (95% CI) Days	*p-value*
Premature	529	42 (7.94)	2 (1.76-2.24)	0.468
Term	361	22 (6.09)	2 (1.82-2.18)	

[a]Kaplan Meier analysis.

Table 3. Factors of treatment failure

Variables	Crude HR[a] (95% CI)	Adjusted HR[b] (95% CI)	*p-value*
Low birth weight	0.02 (0.001-0.69)	0.56 (0.33-0.96)	0.035
Ventilator (CPAP)	11.07 (1.10-111.13)	3.08 (1.38-6.83)	0.006
Hypothermia	2.12 (0.00-2.46)	8.26 (1.56-43.89)	0.013

[a]Simple Cox proportional hazard regression,
[b]Multiple Cox proportional hazard regression. There are interaction and multicollinearity problem.

Table 4. Difference of median treatment duration of treatment success neonates between GA groups

Variables	n	Treatment success (%)	Median (95% CI) Days	*p-value*
Premature	529	487 (92.06)	4.00 (3.86-4.14)	0.353
Term	361	339 (93.91)	3.00 (2.81- 3.20)	

[a]Kaplan Meier analysis.

Table 5. Factors of prolong treatment duration more than 72 hours

Variables	*b* (SE)	Crude HR (95% CI)	*p-value*
Fever symptom	-0.503 (0.228)	0.61 (0.39-0.95)	0.027

Multiple Cox regression.

DISCUSSION

A total of 894 cases started with empiric antibiotic within 72 hours of life for suspected Early Onset Sepsis (EOS). Maternal risk factors and intrapartum complications were the main contributing factors for suspected EOS in neonates. According to recent MMWR recommended report 2010, pregnancy women with risk of infection includes positive rectovaginal culture; chorioamnionitis; prolonged rapture of membranes; and premature delivery should be covered with antibiotic prophylaxis during pregnancy or intrapartumly for prevention of perinatal Group B Streptococcal infection (ACOG, Committee opinion 2011; Verani *et al.,* 2010). Neonates of mothers who received intrapartum antibiotic prophylaxis (IAP) are more likely to be treated for suspected EOS and will prolong hospital stay (Galsgow *et al., 2*007). In our analysis, we found that the use of antibiotic during pregnancy was higher in premature neonates. It's use was also significantly associated with maternal risk factors such as urinary tract or vaginal infections, chorioamnionitis and Prolong Rapture of Membrane (PROM) more than 18 hours ($p < 0.05$). According to reported studies, prematurity are associated with many complications especially increased risk of infections (Verani *et al.,* 2010; Bhat and Baby 2011) and risk of RDS (Hermansen And Lorah 2007). Their immune system and skin barrier are immature and they are exposed to many procedures during NICU admission (Makhoul *et al.,* 2005). Respiratory distress however occurs as a result of underdeveloped lung anatomy and surfactant deficiency (Hermansen and Lorah 2007).

Antenatal steroid was given to mother at risk of premature delivery or elective caesarean prior 38 weeks to prevent RDS since steroid will accelerate fetal lung maturation. It was effective in reducing RDS when delivery occurs after 24 hours and up to 7 days after administration of second dose of antenatal steroid (RCOG, Green-top Guideline 2010). More than 80% of premature neonates had respiratory distress syndrome. Distinguishing neonates diagnosed with RDS from congenital pneumonia is difficult due to the similarity in the presentation of the symptoms. They generally will be treated with empiric antibiotic (Behrman and Butler 2007). Besides antibiotic, neonates diagnosed with RDS were usually managed and treated with oxygenation, ventilation and surfactant replacement (Hermansen and Lorah 2007). The risk of MSAF and perinatal asphyxia were significantly associated with term neonates in this study. It is also associated with high number of cases diagnosed of MAS and Hypoxic Ischemic Encephalopathy (HIE). In general, Meconium Stained Amniotic Fluid (MSAF) will occur in 13% of delivery and at least 5% of those cases presented with Meconium Aspiration Syndrome (MAS). This observation is not unique where other studies had shown it is a normal occurrence in term and post term neonates (Gelfand *et al.,* 2004; Yurdakok 2011).

MAS is usually presented with symptoms of hypoxia and significant respiratory distress after delivery (Hermansen and Lorah 2007). Fits symptom was significantly associated with term neonates in HSA and HPP. This observation could be due to the effect of MAS and HIE in neonates. Nevertheless, the insignificant differences in the occurrences of fits symptoms of HRPB patients could be possibly due to undocumented incidences of perinatal asphyxia. Gerdes, 2004 and Escobar, 1999 states that the practice of ruling out for possible bacterial infection is routine in the Neonatal Intensive Care Unit (NICU) (Gerdes 2004; Escobar 1999). According to National Neonatology Forum (NNF), clinicians need to have high suspicion index in order to start neonates with antibiotics as presumptive treatment. This is because the delay of treatment will increase the risk of mortality (Muller *et al.,* 2011). In this study, more than half of NICU admissions were neonates with suspected sepsis within the 72 hours of life and required empiric antibiotics. Infection usually occurs during or shortly before birth due to the transfer of pathogens colonizing in the mother's genital tract (WHO 2009). It is normally presented as pneumonia, sepsis and less commonly as meningitis. The choice of empiric antibiotics must be driven by clinical or antibiotic guidelines and is dependent on the probable pathogens and strong perinatal history including maternal symptoms and culture (Clark *et al.,* 2006). In our study, 734 (98%) cultures were from blood samples and 18 (2%) were from other sources. However, cultures with proven EOS remained scarce among neonates. The low number of positive cultures observed in the present study of 3.67% (33) was similarly reported by Clark *et al*. (2006) and Metsvaht *et al*. (2010). These findings showed the choices of antibiotics used for EOS in the present studied neonates are effective. Data findings suggested the risk of proven infection was higher in premature neonates (>70%) could be due to their immature immune system. More than 70% of microorganisms isolated in this study were gram positive organism. These findings are different from a previous report where the microorganism that caused EOS was predominantly gram negative (Stoll *et al.,* 2002). It may be due to the lower number of IAP exposure in culture proven sepsis case as mentioned previously.

According to the Clinical Practice Guidelines (2004) endorsed by the Ministry of Health Malaysia (MOH) on the rational antibiotic utilization in selected pediatric conditions, penicillin or ampicillin plus gentamicin are the recommended therapy for neonates with suspected EOS. MOH also published the National Antibiotics Guidelines (NAG) in 2008 to be used as a reference to facilitate antibiotic choice based on infectious type and severity. In this guideline, penicillin or ampicillin plus gentamicin is the recommended regimen of choice for EOS and ampicillin plus cefotaxime was the alternative regimen. Studies comparing the treatment of choice for EOS in neonates are limited (Mtitimila and Cooke 2004). A study by Metsvaht *et al*. in 2010 showed ampicillin/gentamicin and penicillin/ gentamicin regimens were equally effective and no association between empiric antibiotic exposure and effect on gut micro flora. Clark *et al*. in 2006 however showed the use of cefotaxime in the regimen will increase the risk of fungal infection and death. Our study reported that the mean treatment duration for all three hospitals was 3.78, 1.72 (Mean, SD) days. This study showed the appropriate treatment duration because prolonged empiric antibiotic duration more than 5 days may affect the gut colonization and can increase the risk of Necrotizing Enterocolitis (NEC) in neonates (Cotton *et al*., 2009). Besides that, it may also increase the risk of candidiasis especially in LBW neonates (Cotton *et al*., 2006). The practice of discontinuing of empiric antibiotics when blood cultures are negative and no clinical sign is observed in all three hospitals offers an opportunity to reduce antimicrobial exposure and minimize risk of NEC and candidiasis (Leandro and Leona 2003). This practice is further enhanced by the study by Bizzarro *et al*. (2008) where by reducing the empiric antibiotic duration will not increase the risk of relapse and may reduce the incidence of late onset sepsis. A study by Metsvaht *et al*. (2009) reported 10-20% treatment failure in suspected or proven EOS administered with penicillin or ampicillin plus gentamicin antibiotic therapy and premature and LBW neonates may increase risk of treatment failure. In this study, a multivariate analysis was conducted and found LBW as a significant factor for treatment failure ($p < 0.05$). Besides that, requirement for CPAP in 72 hours of life and hypothermia symptom may increase the risk of failure. There was no significant difference in treatment duration for treatment failure among both premature and term neonates. Multivariate analysis however found that the risk of prolonged treatment duration is increased by 0.61 times when neonates had presented with fever initially. The reason is fever was always consider as sign of infections and it will lead to prolonged treatment duration if temperature still uncontrolled after antibiotic exposure.

Conclusion

Current practices showed that, empiric antibiotic regimen recommended by National Antibiotic Guideline (NAG) 2008 Ministry of Health Malaysia were still in use for the management of suspected EOS in all three hospitals. 97% of cases were prescribed with penicillin plus gentamicin regimen and started within 24 hours of life with mean treatment duration less than 4 days. Appropriate use of empiric antibiotic and treatment duration can be seen in this study. Despite the

differences in characteristics and risk between premature and term neonates, empiric antibiotic use showed effective coverage for suspected EOS with overall treatment successful rate of 93%. However, neonates presented with fever have 0.61 times increased risk of prolong treatment duration. Requirement for CPAP, LBW and hypothermia may increase the risk of treatment failure.

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