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Early Onset Neonatal Sepsis Pathogens in Malaysian Hospitals: Determining Empiric Antibiotic

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***Abstract*—**Information regarding early onset neonatal sepsis (EONS) pathogens may vary between regions. Global perspectives showed Group B *Streptococcal* (GBS) as the most common causative pathogens, but the widespread use of intrapartum antibiotics has changed the pathogens pattern towards gram negative microorganisms, especially *E. coli*. Objective of this study is to describe the pathogens isolated, to assess current treatment and risk of EONS. Records of 899 neonates born in three General Hospitals between 2009 until 2012 were retrospectively reviewed. Proven was found in 22 (3%) neonates. The majority was isolated with gram positive organisms, 17 (2.3%). All grams positive and most gram negative organisms showed sensitivity to the tested antibiotics. Only two rare gram negative organisms showed total resistant. Male was possible risk of proven EONS. Although proven EONS remains uncommon in Malaysia, nonetheless, the effect of intrapartum antibiotics still required continuous surveillance.

***Keywords*—**Early onset neonatal sepsis, neonates, pathogens, gram positive, gram negative.

I. Introduction

NEONATAL sepsis is the major cause of hospitalization in neonatal intensive care unit (NICU). It is a significant cause of neonatal morbidity and mortality especially in the first 3 days of life which also defined as early onset neonatal sepsis (EONS) [1], [2].

There are a few antibiotics approaches being used worldwide in order to reduce the burden. First approach is intrapartum antibiotic prophylaxis for mother with risk factors [3]-[8] and second approach is empiric antibiotics for suspected EONS (neonates with high risk or clinical signs) [9]-[11].

EONS is normally caused by microorganisms that colonize the mother's genitourinary tract and occur within 72 hours of life [1]. The most common microorganisms isolated include group B *Streptococcus* (GBS), *Escherichia coli*, coagulase-negative *Staphylococcus* (CoNS), *Haemophilus influenzae* and *Listeria monocytogenes* [1].

Historically, Group B *Streptococcal* (GBS) has become the primary cause of EONS but the incidence has declined through the widespread use of intrapartum antibiotic prophylaxis [12], [13]. Most of the studies from year 2000 onwards have reported the shift of predominantly gram positive microorganism causing EONS to predominantly gram negative especially *Escherichia coli* over time [12], [13].

However, information regarding EONS pathogens may vary between regions. It is crucial to know the common pathogens involved in EONS in our setting to facilitate the choice of antibiotic and improve the EONS management. We conducted multi-centre retrospective review over 899 neonates with suspected EONS to describe the common pathogens isolated in this specific population, to assess current treatment and risk of EONS.

II. Methods

A. Sample Population and Study Design

Records of 899 neonates born in three General Hospitals (Hospital Raja Permaisuri Bainun Ipoh, Hospital Pulau Pinang and Hospital Sultanah Aminah Johor Bahru) in year 2009 until 2012 were retrospectively reviewed. Only neonates with blood cultures taken and documented prior empiric antibiotics administration and within 72 hours of life were included. Blood culture result was traced and documented in designated data collection form.

B. Study Approval

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

C. Statistical Analysis

All data were entered on a SPSS for windows version 16. The frequencies and percentages 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. Logistic-regression models were used to assess associations between proven EONS and neonatal characteristics, maternal characteristics and risk. For all statistical analyses, the significance was set at 0.05.

III. Results

Of 899 suspected EONS reviewed, there were 734 (82%) with documented blood culture taken prior empiric antibiotic within 72 hours of life. Out of it, 22 cases were proven EONS with positive blood culture. Demographics characteristics of suspected and proven EONS were shown in Table I. The male to female ratio was 2.14:1. Malay ethnicity shows the highest number of proven EONS as compared to other ethnics. Both suspected and proven EONS occurred more in premature and low birth weight neonates with mean of gestational age less

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than 37 weeks and birth weight less than 2.5 kg. Length of hospital stay was significantly longer in proven EONS group.

TABLE I
DEMOGRAPHICS CHARACTERISTICS

Characteristics	Suspected EONS n = 712	Proven EONS n = 22	P value
Gender			0.277
Male, n (%)	430 (60.40)	15 (68.18)	
Female, n (%)	282 (39.61)	7 (31.82)	
Ethnic			0.462
Malay, n (%)	449 (63.06)	18 (81.82)	
Chinese, n (%)	119 (16.71)	1 (4.54)	
Indian, n (%)	75 (10.53)	1 (4.54)	
Others, n (%)	69 (9.69)	2 (9.09)	
Gestational age (week), mean (±SD)	34.90 (3.975)	33.19 (4.535)	0.269
Birth weight (kg), mean (±SD)	2.27 (0.841)	1.98 (0.848)	0.113
Length of stay (day), mean (±SD)	17.89 (17.289)	24.59 (19.271)	**0.002***

* There was a significant association between proven EONS and prolongation of hospital stayed.

Table II shows the distribution of pathogens isolated from blood cultures. Gram positive pathogens contribute majority of the proven EONS case, 17 (77.27%) and the remaining were gram negative pathogens, 5 (22.73%). *Coagulase negative staphylococci* (CoNS), *Bacillus sp*. and *Streptococcus pneumoniae* were common isolated that account to more than 60% of total blood cultures isolated. Another 40% were isolated with other pathogens which contributed only one case each. Death was reported in one *Streptococcus pneumonia* case due to invasive infection within 7 days of life.

TABLE II
DISTRIBUTION OF PATHOGENS AMONG 22 CASES OF PROVEN EONS OCCURRING IN 734 SUSPECTED EONS BORN IN THREE GOVERNMENT HOSPITALS BETWEEN 2009-2012

Organism	n (%)
Gram positive organisms	17 (77.27)
Coagulase negative *staphylococci* (CoNS)	7 (31.82)
Bacillus sp.	5 (22.73)
*Streptococcus pneumoniae**	2 (9.09)
Streptococcus spp.	1 (4.54)
Enterococcus sp.	1 (4.54)
Group B *Streptococcal* (GBS)	1 (4.54)
Gram negative organisms	5 (22.73)
Stenotropomonas (xantho) maltophi	1 (4.54)
Haemophilus influenza	1 (4.54)
Spingomonas paucimobilis	1 (4.54)
Enterobacter gergoviae	1 (4.54)
E. coli	1 (4.54)
Total	22 (100)

* One case death within 7 days of life due to invasive infection.

Table III shows the antibiotic susceptibility pattern of isolated pathogens. Only recommended antibiotics for suspected EONS were reported. CoNS shows some cases were resistant to penicillin however, there were highly susceptible to gentamicin. Most of the Bacillus sp. was highly resistant to ampicillin and penicillin however, there were susceptible to gentamicin and cefotaxime. In gram negative pathogens, *Stenotrophomonas (xantho) maltophi* shows resistant to gentamicin and *Enterobacter gergoviae* shows resistant to all tested antibiotics (ampicillin, gentamicin and cefotaxime).

TABLE III
ANTIBIOTIC SUSCEPTIBILITY PATTERN

	Total Case, n	Antibiotic tested (n)			
		Ampicillin	**Penicillin**	**Gentamicin**	**Cefotaxime**
Gram positive					
Coagulase negative *staphylococci* (CoNS)	7	NT (7)	NT (5), R (2)	NT (1), S (6)	NT (7)
Bacillus sp.	5	R (4), NT (1)	R (3), NT (2)	I (1), S (3), NT (1)	NT (4), S (1)
Streptococcus pneumoniae	2	NT (2)	S (1), R (1)	NT (2)	NT (1), S (1)
Streptococcus spp.	1	S	S	S	NT
Enterococcus sp.	1	NT	S	NT	S
Group B *Streptococcal* (GBS)	1	NT	S	NT	S
Gram negative					
Stenotrophomonas (xantho) maltophi	1	NT	NT	R	NT
Haemophilus influenza	1	S	NT	NT	S
Sphingomonas paucimobilis	1	NT	NT	S	NT
Enterobacter gergoviae	1	R	NT	R	R
E. coli	1	S	NT	S	S

NT = not tested, S = sensitive, R = resistant, I = intermediate.

Table IV shows the association between proven EONS and characteristics of neonates, mothers and the risk of EONS. There was no significant association found in this study. However, male, surfactant, caesarean delivery and prolonged rapture of membrane >18 hours were a possible risk of proven EONS.

IV. DISCUSSION

Blood culture is the most common investigations done prior empiric antibiotics administration in the diagnosis of serious infections [14]. The cultures will be incubated up to 5 days but, in modern culturing system the pathogens can be identified within 48 hours [15] and antibiotic use can be de-escalated within 3 days.

However, cultures with proven EONS remained scarce among neonates. The low number of positive cultures observed in the present study of 3% (n=22) was similarly reported by Clark et al. (2006) [10] and Metsvaht et al. (2010) [11]. This study also reported that male was more predominance to get proven EONS which also concordance with previous reports [16].

TABLE IV
CHARACTERISTICS AND THE RISK OF 22 NEONATES WITH PROVEN EONS

Characteristic	Total, n	OR (95% CI)	P value
Neonate			
Gender			
Male*	15		
Female	7	1.34 (0.96-1.87)	0.085
Ethnic			
Malay*	18		
Chinese	1	0.21 (0.03-1.59)	0.130
Indian	1	0.33 (0.04-2.53)	0.287
Others	2	0.72 (0.16-3.19)	0.668
Premature (GA<37 weeks)			
No*	6		
Yes	16	1.19 (0.24-5.87)	0.833
Low birth weight (BW <2.5kg)			
No*	6		
Yes	16	1.86 (0.41-8.50)	0.422
Ventilator			
No*	5		
Intubated	11	0.98 (0.34-2.88)	0.976
CPAP	6	1.11 (0.33-3.71)	0.863
Surfactant			
No*	15		
Yes	7	1.99 (0.79-4.99)	0.145
Maternal			
LSCS			
No*	13		
Yes	9	0.57 (0.24-1.37)	0.208
UTI / vaginal infection			
No*	20		
Yes	2	0.46 (0.05-4.51)	0.504
Maternal fever			
No*	20		
Yes	2	1.00 (0.15-6.63)	0.997
Chorioamnionitis			
No*	20		
Yes	2	1.23 (0.15-10.10)	0.847
Meconium stained amniotic fluid (MSAF)			
No*	18		
Yes	4	0.73 (0.09-6.24)	0.774
Prolonged rapture of membrane > 18 hour			
No*	16		
Yes	6	1.60 (0.62-4.17)	0.334
Perinatal asphyxia			
No*	21		
Yes	1	0.69 (0.09-5.54)	0.724
Intrapartum antibiotic			
Anytime during hospitalization			
No*	17		
Yes	5	1.24 (0.44-3.56)	
Prior delivery			
No*	16		
Yes	6	1.49 (0.55-4.04)	0.432

*Neonates in this category served as the reference group.

As mentioned previously, microorganism isolated in EONS was closely related to maternal genital tract colonization [17]. There are many varieties of microorganisms causing EONS in developing countries. The most common microorganisms reported to be associated with EONS were group B streptococcus (GBS), *Escherichia coli (E. coli)*, enterococcus and *Listeria monocytogenes*. Coagulase negative *staphylococci* (CoNS) normally can be found in both early and late onset neonatal sepsis [2]. Before the era of intrapartum antibiotic prophylaxis (IAP), GBS was the leading cause of mortality and morbidity among neonates [18].

In the three hospitals setting, antibiotics prophylaxis during pregnancy was commonly prescribed to mothers with risk factors for GBS transmission to neonates. For example, mothers with GBS colonization and preterm premature rupture of membrane will be covered for IAP and this may cause prolonged use of IAP [19].

In 1996, the American College of Obstetrician and Gynecologists (ACOG) and Centers for Disease Control and Prevention (CDC) recommended universal screening for all pregnancy women at 35-37 weeks of gestation before being administered with IAP to prevent GBS early onset sepsis [7]. Routine screening for GBS during pregnancy can prevent more cases of EONS compared to the risk based approach [18], [20]. The use of IAP caused marked reduction of GBS infection by 80-95% among neonates [18].

Many studies reported the use of IAP can affect the pattern of microorganism in EOS by increasing in the frequencies of non-GBS or antimicrobial-resistant [21]. The use of any IAP of more than 4 hours was associated with an increase in *E. coli* infection and ampicillin-resistant infection [22]-[24]. This phenomenon happens frequently in premature and LBW especially in very low birth weight (VLBW) neonates [12], [13], [21].

However in this study, only 22.73% of the proven infection cases were exposed to IAP and this could have affected the impact of IAP to these patients. The common antibiotics used in IAP for the present study were injection ampicillin, tablet erythromycin ethylsuccinate, injection cefoperazone, ampicillin/sulbactam and amoxicillin/clavulanate.

Our data findings suggested the risk of proven infection was higher in premature and LBW 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 EONS was predominantly gram negative [22]. It may be due to the lower number of IAP exposure in culture proven sepsis case as mentioned previously.

Overall analysis showed that the number of proven CoNS became the most common isolated gram positive organism. This organism was common organism isolated in birth canal. This finding was similar with the finding reported by Ghotaslou et al. 2007 in Iran [25]. Even though CoNS were commonly reported as blood culture contaminants, it has gained clinical importance as the etiology agents of catheter-associated bacteremia [14].

Minimum inhibitory concentration (MIC) is defined as the lowest concentration of antimicrobial required to inhibit the visible growth of a microorganism after overnight incubation [26]. It is the gold standard for determining the susceptibility of organisms to antimicrobial and being used by diagnostic laboratories to confirm unusual antimicrobial resistance [26].

Antimicrobial susceptibility surveillance plays an important role in determining empiric antibiotic therapy. Many studies show that by interpreting antimicrobial susceptibility data especially in specific infections [27]-[29] or patients [30]-[32] can provide the update on the most effective empirical treatment and subsequently can avoid the emergence of resistances.

In our study, penicillin (n=6) showed the highest reported resistance followed by ampicillin resistance (n=5), gentamicin resistance (n=2) and cefotaxime resistance last (n=1). Higher number of ampicillin resistance cases in this study was consistent with the findings reported by other authors [12], [22]-[24].

Bacillus sp. showed highly resistant to penicillin and ampicillin, however it was sensitive to either gentamicin or cefotaxime. *E. coli* proven infections occurred in one case and was sensitive to all antibiotic tested. This finding contradicts a report where increase in IAP exposure will increase resistant *E. coli* infection [12]. These findings showed the choices of antibiotics used for EONS in the present studied neonates are effective where penicillin or ampicillin plus gentamicin is the recommended regimen of choice for EONS and ampicillin plus cefotaxime was the alternative regimen [33], [34].

V. Conclusion

Proven EONS remains uncommon in Malaysia, only 3% reported in this study and majority isolated pathogens was gram positive organisms. The effect of intrapartum antibiotics still required continuous surveillance. However, this review show that current treatment used for managing suspected EONS was still effective.

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