Original Article

Eastern Journal of Medicine 12 (2007) 6-14

Antimicrobials utilization and outcomes of neonatal sepsis among patients admitted to a University Teaching Hospital in Malaysia

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Abstract. Neonatal sepsis is one of the most common reasons for admission to neonatal units in developing countries and it remains a significant cause of neonatal morbidity and mortality. Antimicrobial treatment of patients with sepsis is often predicated on the general principles of appropriate drug use and information extrapolated from other populations, rather than on evidence-based recommendations specific to these patients. Limited information is available about antibiotics use among neonates with suspected or confirmed sepsis in Malaysia and many regions of the world. This study aimed to explore and describe the clinical characteristics of neonatal sepsis; current pattern of antimicrobial use; the clinical outcomes of neonatal sepsis management; and to estimate the acquisition costs of the most commonly used antimicrobial regimens in the management of the condition. We retrospectively reviewed all cases of neonates admitted with sepsis to the Neonatal Intensive Care Unit (NICU) of Hospital Universiti Sains Malaysia; a university-based teaching hospital for one year. Both descriptive and inferential statistics were used for data analysis where appropriate. Of the 121 neonates included in the study, 89 (73.6%) presented with various risk factors for sepsis prior to or at the time of diagnosis and maternal risk factor was the highest reported (37.2%). About 26% of the neonates had positive culture and sensitivity tests. Of these, methicillin-resistant S*taphylococcus aureus* (MRSA) constituted the most prevalent microbial isolate (22.5%). All the patients received some form of empiric antibiotic therapy and crystalline penicillin G plus gentamicin regimen was the most commonly prescribed empiric therapy (69.4%). There was about 9-fold difference between the acquisition costs of the most widely and the second most widely used regimen (RM 29.32 per patient vs. RM 264.74 per patient). Four patients (3.3%) died during hospitalization in the NICU and 107 (88.4 %) were discharged clinically stable. Early treatment of neonatal sepsis with broad-spectrum antibiotics based on presenting signs and symptoms and clinical history had produced good clinical outcomes. This study has an important implication on guiding policy for developing comprehensive, evidence-based practice guidelines, adherence to which may lead to improved rational antibiotics use, costs reduction and improvement of overall care of patients with neonatal sepsis.

Key words: Neonatal sepsis; clinical characteristics; antibiotics utilization; NICU

1. Introduction

Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia in the first month of life (1). Studies have recorded an incidence of neonatal sepsis varying between 11-24.5 per 1,000 live births in some Asian countries (2). The incidence of early-onset neonatal sepsis, occurring within the first 5 days of life is 1-5 cases per 1,000 live births and it remains a significant cause of neonatal morbidity and mortality (3-6). These infants should therefore receive aggressive course of parenteral antibiotic

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therapy. It is worthwhile to mention *inter alia* that the use of antibiotics is the standard of care in the treatment of pediatric patients with bacteremia or sepsis. A variety of diagnostic tests (complete blood count, acute phase reactants) are commonly obtained, and antibiotics are continued or discontinued based on the results of the laboratory testing, degree of clinical suspicion and cultures (3). The clinical manifestations of neonatal sepsis vary from being specific to subtle, testing the very skills of a pediatrician. Furthermore, the gold standard for detection of neonatal sepsis, the blood culture, is unreliable when intrapartum antibiotics have been administered (3,4). Even when intrapartum antibiotics are not used, postnatal blood cultures fail to detect bacteremia in an appreciable number of cases.

Antimicrobial treatment of patients with sepsis is often predicated on the general principles of appropriate drug us and information extrapolated from other populations, rather than on evidence-based recommendations specific to these patients (7). The importance of appropriate empirical antibiotic coverage is illustrated by studies that document the association between inappropriate selection and increased mortality. Currently, there are no universally accepted guidelines for the most appropriate empiric therapy in patients with sepsis, and recently published recommendations from two sources are quite different (8,9). Studies have documented the unnecessary, injudicious, or excessive use of antibiotics practices that have led to an alarming rise in antibiotics resistance, which poses a major threat to public health the world over. Some studies have demonstrated that resistance is directly associated with selection of inappropriate antimicrobials and increased patients' mortality (10). Improved guidelines for antibiotic treatment in sepsis neonatorum from institutional etiology and microbial sensitivity should therefore be drawn and enforced.

Neonatal sepsis is one of the most common reasons for admission to neotatal units in developing countries (11) and 'rule out sepsis' is the most common discharge diagnosis from the Neonatal Intensive Care Units (NICU). (4) Limited information is available about evidence-based or even empiric antibiotics use among neonates with sepsis in Malaysia and many regions of the world. Our objectives were to explore and describe the clinical characteristics; current pattern of antimicrobials prescribing practices and utilization in neonates with sepsis; the clinical outcomes of neonates treated with various antibiotic regimens; and to estimate the acquisition costs and financial implications of the most commonly used regimens in the management of the condition at a university teaching hospital in Malaysia.

2. Materials and methods

2.1. Study design and population

This was a cross-sectional study that retrospectively reviewed cases of patients with neonatal sepsis admitted to the NICU of Hospital Universiti Sains Malaysia (HUSM) - a university-based teaching hospital located in Kubang Kerian, Kelantan State of Malaysia. Data were collected from the medical record office of the hospital, based on computerized discharge diagnosis of neonates treated as cases of sepsis from January 1 to December 31, 2002. This was the most recent year with completely stored data available at the time of the study.

2.2. Sampling procedure

Subjects were conveniently selected into the study based on availability of data. Neonates were included in the study based on the following fundamental criteria for sample selection: (i) computerized medical record system showed a discharge diagnosis of neonatal sepsis in patients aged 1-30 days, admitted to the NICU within the stipulated period; (ii) records noted signs and symptoms and/or risk factors that might have predisposed the neonates to sepsis (perinatal or postnatal); (iii) confirmed or suspected diagnosis of neonatal sepsis written in the medical record by a physician; and (iv) the patient had received treatment with any antibiotics regimen. A subject must meet all the four listed criteria for inclusion in the study. Neonates diagnosed by clinicians as cases of nosocomial sepsis and other serious complications were excluded from the study. After a thorough scrutiny, 121 neonates fulfilled the inclusion criteria and were selected for the study.

2.3. Diagnostic criteria for neonatal sepsis

The criteria for the diagnosis and treatment were based on the following:

I. Neonatal and maternal risk factors
II. Clinical signs and symptoms in the neonate
III. A panel of laboratory investigations (microbial cultures, WBC indices and plasma C-reactive protein levels).

The maternal risk factors which placed the neonates at a greater risk of sepsis and used as diagnostic criteria included: premature labour and delivery; prolonged rupture of membranes

Table 1. Clinical signs and symptoms in neonates with sepsis at HUSM

Clinical presentation	n (%)
RD, apnea, grunting, cyanosis	22 (18.2)
None	15 (12.4)
Jaundice	13 (10.7)
Feeding difficulty, vomiting, abdominal distension	12 (9.9)
Fever, hypothermia /RD, apnea, grunting, cyanosis	11 (9.1)
RD, apnea, grunting, cyanosis /jaundice	10 (8.3)
Fever, hypothermia /RD, apnea, grunting, cyanosis/ jaundice	10 (8.3)
Fever, hypothermia	10 (8.3)
Miscellaneous	7 (5.8)
Fever, hypothermia / jaundice	5 (4.1)
Fever, hypothermia / jaundice / miscellaneous	4 (3.3)
Tachycardia, bradycardia, shock	2 (1.7)
Total	121 (100.00)

RD = respiratory distress

(more than 24 hours); antenatal steroids; chorioamnionitis; and manipulative operative delivery. On the other hand, the following factors greatly increased the vulnerability of a neonate to have sepsis at early or late onset and were considered as additional risk factors: perinatal asphyxia; low birth weight; prematurity; invasive procedure; and congenital anomalies. Blood culture was used as the gold standard for the diagnosis of neonatal sepsis in this setting. In addition, C-reactive protein (C-RP) was used as a rapid identification method that helped in the early identification of neonatal bacteremia.

2.4. Data collection procedure

Prior approval for the conduct of the study was obtained from the HUSM's Ethics Committee for the conduct of study in human subjects. The collection of data was done via a thorough review of the past medical records of the study population and the selected subjects. The data were then recorded manually on standardized data collection forms. Data pertaining to patients' demographics (gender, age, birth weight and race); risk factors; clinical presentations; diagnosis of sepsis; antibiotic treatment regimens in the NICU; and clinical outcomes (duration of improvement in the signs and symptoms of sepsis, duration of antibiotics usage, length of stay in the NICU, overall clinical status on discharge and laboratory investigations on discharge) were generated. Antibiotics (drugs acquisition) cost determinations for two most widely used regimens were conducted to obtain an idea of antibiotics regimens acquisition costs for neonatal sepsis management from the hospital's perspective. Costs were determined per patient in Ringgit Malaysia (RM) (exchange rate as at 2002: US$1.00 = RM 3.80).

2.5. Statistical analysis

All data were stored and analyzed using SPSS version 10.1 computer program (SPSS Inc., Chicago, IL). Both descriptive and inferential statistics were used for data analysis as appropriate. Summary of statistics including mean, standard deviation, and range were generated whenever appropriate. All data were tabulated or presented graphically as necessary. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Demographic characteristics of patients with neonatal sepsis

For the year 2002, there were 251 neonates treated for neonatal sepsis according to the computer do cumented records of the Medica

Table 2. Risk factors for neonatal sepsis among neonates admitted at HUSM

Risk factor (s)	n (%)
Maternal risk only	45 (37.2)
None	32 (26.4)
Prematurity only	16 (13.2)
Perinatal asphyxia only	11 (9.1)
Maternal risk with prematurity	10 (8.3)
Maternal risk with perinatal asphyxia	5 (4.1)
Others	2 (1.7)
Total	121 (100.0)

Record Unit (*Unit Rekod Perubatan*) of HUSM, but only 121 neonates fulfilled the eligibility criteria and were included in this study. Majority of the patients were male, constituting about 58 % (70/121). One hundred and twelve (92.6%), 8 (6.6%), and one (0.8%) were Malay, Chinese and Indian, respectively. The mean age (±SD) of the patients was 2.51 ± 4.41 days (range 1 to 29 days) and their mean birth weight (±SD) was 2.75 ± 0.63kg.

3.2. Disease factors and diagnosis of neonatal sepsis

Fifteen (12.4%) of the neonates had no any signs and/or symptoms of neonatal sepsis. Respiratory distress associated with apnea, grunting and cyanosis was the most common clinical presentation (18.2%), followed by jaundice (10.7%), whereas tachycardia or bradycardia associated with shock was the least common presentation (1.7%). Details are provided in Table 1. Of the 121 neonates, 89 (73.6%) presented with various risk factors for sepsis with maternal risk factor as the highest reported (37.2%), whereas the rest had no any risks of sepsis prior to or at the time of diagnosis (Table 2). C-RP concentration determinations were conducted in 114 neonates (94.2%) and 41.23 % of these had positive titer values. Furthermore, the culture and sensitivity results showed: no isolates (negative culture) in 88 (72.7 %) of the patients and different types of microbial isolates (positive culture) in about 31 (25.6%) of the neonates. For an unforeseen reason, the culture and sensitivity (C&S) test was not done in two patients (1.7%). Among those with positive culture tests, methicillin-resistant S*taphylococcus aureus* (MRSA) constituted the most prevalent microbial isolates (22.5% of neonates with positive culture tests), whereas 'mixed bacterial growth' (*Group B Streptococci* and *Bacillus spp*) was isolated in 3.2% of the subjects with positive cultures (Table 3).

Table 3. Types of microbe(s) isolated from blood samples

Microbe (s) isolated	n (%)
Klebsiella spp	3 (9.7)
MRSA	7 (22.5)
MRSE	3 (9.7)
Bacillus spp	2 (6.5)
Mixed bacterial growth (Group B *Streptococci* + *Bacillus spp*)	1 (3.2)
Mixed bacterial and fungal growth	4 (12.9)
Candida spp	2 (6.5)
Pseudomonas aeruginosa	3 (9.7)
Miscellaneous	6 (19.4)
Total	31 (100.0)

MRSA = Methicilline-resistant Staphylococcus aureus; MRSE = Methicilline-resistant Staphylococcus epidermidis; spp = species

3.3. Antibiotics treatment regimens

All the patients were empirically treated with certain antibiotic regimens, pending C&S results. It was evidently clear from the data that the proportion of neonates who received initial empiric therapy with "crystalline penicillin G plus gentamicin" only regimen was the highest (69.4 %), followed by the proportion of those who received "crystalline penicillin G plus gentamicin" initially and "piperacillin plus netilmicin" as second line regimen (14 %).

Table 4. Empiric antimicrobial regimens for neonatal sepsis during NICU stay

Initial regimen	2nd Line regimen	3rd Line regimen	n (%)
C-pen + Genta	-	-	84 (69.4)
C-pen + Genta	Pipera + Netil	-	17 (14.0)
Other combinations	-	-	6 (5.0)
Ampicillin + Genta	-	-	6 (5.0)
C-pen + Genta + Metro	-	-	4 (3.3)
Ampicillin + Genta + Metro	-	-	3 (2.5)
C-pen + Genta	Pipera + Netil	Imipenem	1 (0.8)
Total			121 (100.0)

C-pen = Crystalline penicilline; Genta = Gentamicin; Pipera = Piperacillin; Netil = Netilmicin; Metro = Metronidazole.

Table 5. Culture and sensitivity-directed antimicrobial regimens for neonatal sepsis during NICU stay

Initial regimen	2nd Line regimen	3rd Line regimen	n (%)
Vanco	Metro	-	8 (30.8)
Other combinations	-	-	5 (19.2)
C-pen + Genta	-	-	3 (11.6)
Pipera + Netil	Imipenem	-	3 (11.6)
Pipera + Netil	-	-	2 (7.7)
Pipera + Netil	Vanco	-	2 (7.7)
Pipera + Netil	Ampho. B + Vanco	Fluconazole	1 (3.8)
Pipera + Netil	Ceftazidime	-	1 (3.8)
Ampho. B + Imipenem + Metro	-	-	1 (3.8)
Total			26 (100.0)

Vanco = vancomycin; Metro = metronidazole; C-pen = crystalline penicilline; Genta = gentamicin; Pipera = piperacillin; Netil = netilmicin; Ampho. B = amphotericin B.

Imipenem was rarely added to the latter in only about 0.8 % of the study population. The trend of empiric antibiotic therapies received by the patients is presented in Table 4. Neonates with positive culture received C&S-directed antibiotic therapies (refer to Table 5).

3.4. Relationship between signs/symptoms and durations of antibiotics treatment

Table 6 indicates that patients with tachycardia, bradycardia, and shock had the highest duration of antibiotics usage, followed by patients who presented with respiratory distress, apnea, cyanosis and jaundice. However, patients without any sign and/or symptom had the least duration of antibiotics usage (4.33 days). Inferential analysis using One-way ANOVA showed that there was no statistically significant difference between different categories of signs and symptoms with respect to the duration of antibiotics use (*p*-value 0.094).

3.5. Antibiotics costs determination

Acquisition costs of antibiotics (Level 1 costs) from hospital's perspective were determined. The total estimated costs of the most widely used regimen comprising crystalline penicillin and gentamicin was RM 2,580.49, equivalent to RM 29.32 per patient (Year 2002 value of RM). An estimated acquisition cost of RM 4,500.62, equivalent to RM 264.74 per patient (Year 2002 value of RM) was expended for the second most widely used regimen (crystalline penicillin plus gentamicin, followed by piperacillin plus netilmicin).

3.6. Overall clinical status of neonates on discharge

The overall clinical outcomes of the treatment of neonatal sepsis showed that 88.4% of the patients were clinically stable on discharge and the mortality rate was 3.3%.

Table 6. Signs and symptoms of neonatal sepsis and duration of antimicrobial use

Presenting signs/symptoms	n (%)	Mean duration of antibiotics	*p value
			0.094
Fever, hypothermia	10 (8.3)	4.40	
RD, apnea, grunting, cyanosis	22 (18.2)	7.23	
Tachycardia, bradycardia, shock	2 (1.7)	17.00	
Jaundice	13 (10.7)	7.31	
Feeding difficulty, vomiting, abdominal distension	12 (9.9)	7.08	
Miscellaneous	7 (5.8)	8.43	
Fever, hypothermia /RD, apnea, grunting, cyan /jaundice	10 (8.3)	7.40	
Fever, hypothermia, jaundice	5 (4.1)	6.80	
RD, apnea, grunting, cyanosis / jaundice	10 (8.3)	9.70	
Fever, hypothermia / RD, apnea, grunting, cyanosis	11 (9.0)	6.18	
None	15 (12.4)	4.33	
Fever, hypothermia /jaundice /miscellaneous	4 (3.3)	7.25	
Total	121 (100)	-	

RD = respiratory distress. * One Way ANOVA test

4. Discussion

The dominance of the Malay ethnic group in the study population might not be unrelated with the fact that the State of Kelantan is dominated by the same race. Physicians in small, ill-equipped or resource-constrained centers manage many neonates in developing countries, and they have to depend on clinical signs alone for diagnosis (12). In this study, respiratory distress associated with apnea, grunting and cyanosis was the most prevalent sign of clinically suspected sepsis (18.2%). Other studies have reported closely similar results to these observations (12,13). Currently, there is lack of definite consensus among neonatologists on several aspects of diagnosis and treatment of hospitalized neonates with suspected early or late-onset sepsis. Anticipation from the clinical history, suspicion from the clinical findings and confirmation by preliminary laboratory studies are essential for intact survival of the neonate. Therefore, clinical suspicion forms the starting point for the management of neonatal septicemia, but clinical signs in the newborn are notoriously unreliable (14). Risk factors also form the basis for diagnosis and treatment of neonatal sepsis. Treatment guidelines advocate that antibiotics should be considered in any baby with sign of sepsis, particularly in the presence of risk factors. This study found that 37.2% of the neonates had maternal risk factors. Babies with prematurity and perinatal asphyxia constituted 13.2% and 9.1% of the subjects, respectively. Neonates, especially premature babies, are predisposed to infection as they are deficient in host defenses and are at risk of acquiring infections from mothers during perinatal periods (11). The pathogenesis of early onset bacteremia involves the complex interaction of maternal-fetal colonization, transplacental immunity, and physical and cellular defenses of the fetus and the mother. Studies have repeatedly identified prematurity, prolonged rupture of membranes and maternal chorioamnionitis as risk factors for congenital bacteremia.

Among the most important protocols for the diagnosis of sepsis is blood C&S, which is considered as the gold standard (15). In compliance with the universal diagnostic protocols, 98.3% of the neonates had their blood tested for culture. Out of this, about 26% had positive culture results, hence definite or confirmed sepsis. In addition, the most prevalent microbial isolates were MRSA and MRSE (32.2% of those with positive culture). The preponderance of negative blood cultures in about 72.7% of the neonates was not a guarantee to 'rule-out' sepsis, since blood culture test was reported to be unreliable (3,16). *Klebsiella* species, *Pseudomonas aeruginosa*, and Candida species were among other isolates detected by blood C&S. In a study by Jaswal, however, it was narrated that the incidence of blood culture positivity was 42 %, out of which 23.8% was *Klebsiella* species followed by *E. coli* (19.04%)

(5). Meanwhile numerous studies have reported that the most common organisms implicated in early-onset sepsis are *Group B Streptococci, Staphylococcus aureus, Eschericia coli, Klebsiella spp, Hemophilus influenza, Listeria monocytogenes* (11,17-19). This signifies that the pattern of bacterial isolates may differ from one geographical region to another, one institution to another and use of different antibiotics at different centers may be warranted.

Furthermore, reliable and accurate markers that identify infants with neonatal sepsis are needed to reduce unnecessary use of antibiotics and the risk of emerging bacterial resistance in newborn nurseries (20). C-RP determination has high negative predictive accuracy of more than 99%. Hence, it is a very useful parameter in neonatal sepsis diagnosis and management (3,21-23). At HUSM it has become the standard of practice to conduct C-RP test for neonates suspected to have sepsis and in monitoring their therapies. In this study, C-RP was measured in more than 90% of neonates and nearly half of these had positive titer values. Overall, at the time of final diagnosis, 31 episodes (25.6%) were confirmed as 'definite sepsis', whereas about 74 % were still 'probable' (same as initial diagnosis). Both suspected and confirmed cases were included in this study having in mind that, the blood culture was not a fool-proof standard and should not be used as a standalone procedure for clinical decision (3,12,16).

Neonatal sepsis is a life-threatening emergency and any delay in treatment may result in death (24). Infants with suspected sepsis are treated with broad-spectrum antibiotics, while blood culture results are pending. The standard of practice in most parts of the world is to commence empiric antibiotic therapy with a penicillin and an aminoglycoside, while taking into consideration the institutional-based antibiograms that show susceptibility pattern (25,26). From this study, it was found that all the patients were empirically treated and the vast majority had received a regimen of crystalline penicillin and gentamicin, pending the results of blood culture. Antimicrobial selection was usually empirical in view of the need to initiate treatment before C&S results were available and because in many patients with sepsis no pathogen is isolated (7).

Findings from this study points to excessive use of prophylactic antibiotics. This is evident from the fact that a large proportion of the neonates in this setting were treated due to high risk of sepsis or high index of clinical suspicion without documented bacteriologic evidence of sepsis. This may reflect the wide variation in the incidence of invasive disease, lack of guidelines supporting a role for prophylaxis and concerns related to the emergence of resistant strains of microorganisms. Furthermore, there is insufficient evidence from randomized trials to support or refute the use of prophylactic antibiotics in neonatal sepsis. In these patients, in addition to routine microbiological culture, molecular methods used in the diagnosis of microorganism will provide rapid and reliable diagnosis. As a result, the disease must be diagnosed quickly and the routine use of antibiotics would be in place, but microbiological cultures must be the gold standard methods to rule out infection in newborn infants with neonatal sepsis and for the decision whether the use of antibiotics will be continued. A major concern is the emergence of antibiotics resistance if the practice deviates from this norm. Usually, very broad-spectrum therapy is used initially because of the need for coverage of a wide range of potential pathogens. Still, the selection of initial therapy should be approached in a rational and considerate manner that takes into account some specific factors and if possible based on the best evidence. For infants with suspected sepsis whose cultures are sterile after 48-72 hours of antibiotics and whose subsequent clinical course does not suggest sepsis, discontinuation of therapy is warranted (1,27). The second most commonly used regimen at our setting was still the use of the crystalline penicillin and gentamicin as the first line, followed by piperacillin plus netilmicin as a second line regimen. However, some regimens used were apparently inappropriate without any foreseeable rationale, in that they neither obeyed the general principle of antibiotics selection nor were they evidence-based. Selection of antimicrobials in NICU should be further informed by formulary decisions and practice guidelines. The importance of prudent selection of antibiotics cannot be overemphasized due to changes in the spectrum of organisms that cause neonatal sepsis over time and most importantly due to the public health threat posed by drug resistance. It is noteworthy that about 6.6% of the entire study population (31 % of patients with positive culture) was treated with vancomycin, followed by metronidazole. This was consistent with the fact that MRSA and MRSE were the most prevalent isolates among those with positive culture and supported by the recommendations of other studies (19,24). Overall, 107 neonates (88.4%) were clinically stabel at the time of discharge, whereas 4 patients (3.3%) died.

It is worthwhile to mention that in 2004 a national guideline on rational antibiotics utilization in selected pediatric conditions was developed in Malaysia (26). The aim of the guideline was to aid general practitioners and pediatricians in clinical decision making by providing well-balanced information on the rational utilization of antibiotics in common pediatric conditions. In this, a section was dedicated to neonatal sepsis. Although neither exhaustive nor exclusive, the guideline has given a vignette of the clinical presentations, diagnosis, and management of neonatal sepsis. It ended with a set of recommendations and a simplified algorithm for the treatment of the condition. Perhaps this effort would serve as a building block for more comprehensive, evidence-based and consensus-driven guidelines for the management of neonatal sepsis in the future.

The total estimated cost of the most widely used antibiotics regimen, received by 88 infants (69.3% of the study population) over an average period of 5.65 days was RM 2,580.49 (Year 2002 RM; equivalent to US$ 679.08). This was without any consideration to consumables and several other direct and indirect costs. More so, no consideration was given to the actual quantities of drugs dispensed, but rather the actual doses administered to the patients. Paradoxically, an estimated acquisition cost of RM 4,500.62 (equivalent to US$ 1,184.37) was expended on the second most widely used regimen for only 17 neonates (14% of the study subjects). This signifies RM 29.32/patient (US$ 7.72/patient) for the most widely used regimen vs. RM 264.74/patient (US$ 69.67/patient) for the second most widely used regimen. The dramatic relative increase in cost may be due to the excessive prices of piperacillin and netilmicin. Due to the methodological limitations inherent to pharmacoeconomic studies of infectious diseases (28) and time constraints, our costs descriptions were merely for the determination of the acquisition costs of anti-infective agents. In this, the primary focus was not to provide an economic evaluation of treating neonatal sepsis and the major limitation was the failure to consider the majority of expenditures associated with the treatment of an infectious episode.

Hence, there could be gross underestimations of costs and future studies need to be rigorously designed to look into this. Furthermore, the costs data were collected from the pharmacy department and the account unit databases, which may not be applicable and generalizable to other institutions. This study has highlighted an important clinical condition in which there are limited available scientific evidences on its management and guideline on how judicious antibiotics utilization could improve clinical outcomes and lower financial burdens. However, the study had encountered a number of limitations; mainly, the retrospective design had plausibly limited the spectrum of the study in exploring many relevant parameters.

The results of this study have delineated a practice area in which there is lack of consensus; in fact, an area of serious diagnostic and therapeutic dilemma. Consequently, the need for comprehensive, evidence-based clinical practice guidelines for the management of neonatal sepsis in NICU setting is highly warranted.

The findings could be the bedrock for designing a more robust research in both clinical and economic aspect of this life-threatening emergency in the future. In the mean time, the hospital could impose certain strict criteria and protocols with respect to initiation of empiric antibiotics therapy based on the scanty data in the existing national guideline.

Early treatment of neonatal sepsis with broad-spectrum antibiotics based on presenting signs and symptoms and clinical history had produced good clinical outcomes and perhaps shortened the length of NICU stay. In accordance with the findings, empiric antibiotics prescribing practices in NICU seemed to be somewhat similar to those reported by other studies in similar settings. However, some regimens were seemingly used inappropriately without any rationale. Conclusively, the selection of antimicrobials in NICU should be based on formulary decisions and evidence-based practice guidelines.

Acknowledgements

We are deeply indebted to the staff of *Unit Rekod Perubatan* at HUSM, Madam Mariani Bt. Hj. Yaacob of Pharmacy Department, Madam Razuna Zaky, Madam Norul Badriah Hassan for providing us with data and an enabling environment to conduct this study.

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