Original Article

Etiological patterns of bacterial meningitis in neonatal sepsis

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ABSTRACT

Background Sepsis and meningitis are major causes of mortality and morbidity in neonates. The prevalence of sepsis is around 1-4 out of every 1000 live births, and one-fourth is accompanied by meningitis. These numbers are higher in prematures.

Objective To find out the prevalence and etiological patterns of bacterial meningitis in neonatal sepsis, and the pattern of antibiotic susceptibility for organisms causing bacterial meningitis.

Methods This was a cross sectional study, conducted in the neonatal ward and emergency room at Cipto Mangunkusumo Hospital from October 2003 to October 2004.

Results Seventy two neonates fulfilled the inclusion criteria and were examined for blood and cerebrospinal fluid (CSF) cultures. Sixty out of 72 neonates were proven for sepsis. Bacterial meningitis was found in 18 neonates, and all cases were accompanied by sepsis. Positive CSF cultures were found in 12 neonates. The other six were diagnosed based on CSF cell count $\geq$32/µl. *Acinetobacter calcoaceticus* was the major causative organisms in this study. The organisms were highly resistant to first line antibiotics, except for chloramphenicol. They were also sensitive to ceftazidime (second line), meropenem, and imipenem.

Conclusions The prevalence of bacterial meningitis in neonatal sepsis at Cipto Mangunkusumo Hospital was 18/60 in 2003-2004. The major causative organism was *Acinetobacter calcoaceticus*. Antibiotic resistance was very high and only chloramphenicol, ceftazidime, meropenem, and imipenem remain effective **[Pediatr Indones 2006;46:32-36].**

Keywords: bacterial meningitis, neonates, neonatal sepsis

than at any other time of life, which is about 0.25-1/1000 live births. Twenty five percent of neonatal sepsis will also have positive cerebrospinal fluid (CSF) cultures.[3] Bacterial meningitis in neonates is quite different with those in older children and adults. The absence of specific clinical findings makes diagnosis of meningitis in neonates more difficult than that in older children or adults. Moreover, a wide variety of pathogens are seen in infants because of the immaturity of their immune system. Advances in neonatal intensive care have resulted in the increasing number of surviving infants, especially prematures who are hospitalized longer and therefore have a higher possibility to acquire infections. Bacterial meningitis requires serious attention because of its severe neurological sequelae which may impair the surviving infants' quality of life. Early intervention is very essential to gain better prognosis, thus empirical aggressive antibiotics treatment plays a major role in neonatal bacterial meningitis. Information about the prevalence and likely pathogens are very important, since empirical antibiotics should include agents which are active against most suspected organisms.

S epsis and meningitis are major causes of mortality and morbidity in neonates despite the advances in neonatal intensive care medicine.[1,2] The prevalence of meningitis in the neonatal period is more frequent

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This study aimed to find out the prevalence of neonatal bacterial meningitis along with the causative organisms and their susceptibility to antibiotics.

Methods

This was a cross-sectional study done at Cipto Mangunkusumo Hospital, Jakarta, Indonesia which included all neonates born during October 2003-October 2004, suspected for late onset sepsis (>72 hours), or early onset sepsis with positive blood culture or central nervous system (CNS) signs, or planned to undergo repeated septic work-up because of clinical deterioration. Exclusion criteria were severe cardio- respiratory compromise or severe congenital CNS abnormality.

Subjects were recruited consecutively up to a sufficient number. All subjects underwent blood culture, CSF culture, and complete CSF examination. CSF and blood cultures were obtained using Bac-T alert transport media and incubated in Microbiology Laboratory, Clinical Pathology Department, Cipto Mangunkusumo Hospital. Sepsis was diagnosed based on positive blood cultures, and meningitis was diagnosed based on positive CSF cultures and/or CSF pleiocytosis ($\geq$32 cells/μl).

This study was approved by The Committee of Medical Research Ethics, Medical School, University of Indonesia. Informed consent from parents or other family members were obtained prior to the study.

Results

During a one year study period, there were 3289 live-births in Cipto Mangunkusumo Hospital. There were 72 patients who fulfilled the inclusion criteria. Sixty of these were proven for sepsis and included in the analysis.

Forty-six out of 60 subjects were hospitalized in the perinatal ward. Male subjects were more than female ones with a 1.22:1 ratio. A complete description of subjects' characteristics can be found in **Table 1**.

Eighteen out of 60 subjects with proven sepsis were diagnosed with meningitis. Twelve of these 18 patients had positive CSF cultures, and the remaining were diagnosed as meningitis based on CSF pleiocytosis ($\geq$32/μl). Therefore, the prevalence of bacterial meningitis in neonatal sepsis was 18/60. We found no cases of isolated meningitis without sepsis.

The etiologic organisms of sepsis and meningitis can be found in **Table 2**. *Acinetobacter calcoaceticus* was the most frequent causative organism for both sepsis and meningitis in this study.

The Microbiology Division of the Clinical Pathology Department at Cipto Mangunkusumo Hospital divided antibiotics tested for sensitivity into first line, second line, and special antibiotics. Sensitivity patterns can be seen in **Table 3** and **Table 4**.

Most organisms which cause bacterial meningitis were resistant to first line agents, except for

TABLE 1. CHARACTERISTICS NEONATES WITH SEPSIS (N=60)

Characteristics	n
Nurseries	
Emergency Room	14
Perinatology Ward	46
Sex	
Male	33
Female	27
Birth weight (range 1100-4050 grams; mean 2476.5±774.2 g)	
<1000 g	-
1000-1499 g	10
1500-2499 g	14
2500-3999 g	35
$\geq$4000 g	1
Gestational age (range 28.5-42 weeks; mean 36.7±3.4 weeks)	
<28 weeks	-
28-32 weeks	9
33-36 weeks	12
37-42 weeks	39
>42 weeks	-

TABLE 2. ORGANISMS CAUSING SEPSIS AND MENINGITIS

Microorganism*	Sepsis (n)	Meningitis (n)
A. calcoaceticus	28	7
K. pneumoniae	11	1
E. aerogenes	8	1
S. marscescens	6	1
Pseudomonas	3	1
S. epidermidi	3	-
S. aureus	1	-
E. gergoviae	-	1
Total	60	12

* No multiple infections were found in all subjects. There were six other subjects that were diagnosed for meningitis based on CSF pleiocytosis $\geq$32/μl

TABLE 3. SUSCEPTIBILITY OF FIRST AND SECOND LINE ANTIBIOTICS FOR ORGANISMS CAUSING BACTERIAL MENINGITIS

Microorganism	OXA	AMX	AMP	CHL	GEN	AMK	SAM	CTX	AMC	CTR	CIZ*	VAN
A. calcoaceticus 1	R	R	R	S	R	S	R	R	R	R	S	R
A. calcoaceticus 2	R	S	S	S	S	S	S	S	R	S	S	R
A. calcoaceticus 3	R	R	R	S	R	R	R	R	R	R	S	R
A. calcoaceticus 4	R	R	R	R	S	S	S	R	I	R	R	R
A. calcoaceticus 5	R	R	R	S	R	R	R	R	R	R	S	R
A. calcoaceticus 6	R	R	R	S	R	R	R	R	R	R	S	R
A. calcoaceticus 7	R	R	R	S	R	R	R	R	R	R	S	R
K. pneumoniae	R	R	R	R	R	I	R	R	R	R	R	R
E. aerogenes	R	R	R	S	S	S	R	R	I	R	R	R
S. marscescens	R	R	R	S	I	S	S	S	S	S	S	R
Pseudomonas	R	R	R	R	R	R	R	R	R	R	S	R
E. gergoviae	R	R	R	R	R	R	R	R	R	R	R	R

R=resistant, I=intermediate, S=sensitive. First line antibiotics: oxacillin (OXA), amoxycillin (AMX), ampicillin (AMP), chloramphenicol (CHL), gentamcin (GEN). Second line antibiotics: amikacin (AMK), ampicillin-sulbactam (SAM), cefotaxime (CTX), amoxycillin-clavulanic acid (AMC), ceftriaxone (CTR), ceftazidime(CIZ), vancomycine (VAN). *Ceftazidime is the first line antibiotic used in Perinatology Division, Cipto Mangunkusumo Hospital.

TABLE 4. SUSCEPTIBILITY OF SPECIAL ANTIBIOTICS FOR ORGANISMS CAUSING BACTERIAL MENINGITIS

Microorganism	TCY	FEP	IMI*	MRM*	FOS
A. calcoaceticus 1	R	R	S	S	R
A. calcoaceticus 2	R	S	S	S	S
A. calcoaceticus 3	R	I	S	S	R
A. calcoaceticus 4	R	S	S	S	S
A. calcoaceticus 5	R	R	S	S	R
A. calcoaceticus 6	R	R	S	S	R
A. calcoaceticus 7	R	S	S	S	R
K. pneumoniae	R	R	S	S	S
E. aerogenes	R	I	S	S	S
S. marscescens	R	S	S	S	R
Pseudomonas	R	R	S	S	R
E. gergoviae	R	I	S	S	S

R=resistant, I=intermediate, S=sensitive; teicoplanin (TCY), cefepime (FEP), imipenem (IMI), meropenem (MRM), fosfomycine (FOS). *Imipenem and meropenem were second line antibiotics used in Perinatology Division, Cipto Mangunkusumo Hospital.

chloramphenicol. The only second line antibiotic which remains to have sensitivity is ceftazidime. For special antibiotics, imipenem and meropenem showed 100% sensitivity to all causative organisms.

Discussion

Male subjects were more than female with a ratio of 1.22:1. This was in accordance with a previous study by Holt *et al*,[4] who obtained a male to female ratio of 1.2:1 from 274 neonates. The average birthweight was 2476.5±774.2 grams and the average gestational age was 36.7±3.4 weeks. These findings were quite different from a study in Taiwan by Chang *et al*,[5] who found that the average birthweight and gestational age were 3093.5±500.4 grams and 38.9±1.9 weeks, respectively. These differences can be explained from the amount of preterm babies included in both studies. In this study, there were 21 preterms out of 60 babies while in Chang's study there were only 10 out of 60.

Most of the subjects' birth weight and gestational age were between 2500-3999 grams and 37-42 weeks, respectively. There were no subjects with birth weight less than 1000 grams or born before 28 weeks. Most of these neonates experienced severe cardio-respiratory compromises, so lumbar puncture can not be performed. Stoll *et al*,[6] also stated in his study that most neonatologists often defer to perform lumbar puncture in extremely low birth weights (ELBW) since the risk of the procedure is very high.

In this study, the prevalence of neonatal sepsis was 60 out of 72 neonates with suspected sepsis. The prevalence of meningitis was 18/60 of sepsis subjects. This finding was similar with other studies which found bacterial meningitis in 10-25% neonatal sepsis.[2,3,7]

In this study, there were no cases of meningitis without sepsis. Another study by Wiswell *et al*,[7] found 16 out of 43 cases of neonatal meningitis without sepsis. This difference was due to different inclusion criteria. In the present study, lumbar puncture was only

performed in symptomatic neonates, while Wiswell *et al* performed lumbar puncture in asymptomatic neonates with risk factor for sepsis as well.

There were 6 subjects with CSF pleiocytosis and negative CSF cultures in this study. Several conditions could affect this result. Firstly, most of the subjects in this study had already received antibiotics prior to lumbar puncture. Lumbar puncture was performed as part of a repeated septic work-up for these patients, because there were clinical deterioration with first antibiotic. Secondly, there were always possibilities for other causative agents that were not evaluated in this study, like virus or fungus. Viral or fungal infection in CNS can produce pleiocytosis with negative bacterial CSF culture. In the present study by Holt,[4] he found 66 out of 96 sterile CSF subjects with cell count $\geq100/\mu$l. Most CSF samples suspected for meningitis which were negative for bacteria, came out positive with viral culture.

In the present study, there were 12 subjects with positive CSF culture. Not all of them were accompanied by pleiocytosis ($\geq32/\mu$l). Previous study by Nel[8] also showed similar findings which found 6 out of 88 cases of culture proven bacterial meningitis with normal CSF findings. Experts proposed thoughts that there were possibilities that lumbar puncture was performed in early period of infection process. At that time, there were already bacteria in the CSF, but inflammation process that caused pleiocytosis has not yet occured.[9]

Our study found *Acinetobacter calcoaceticus* as the most frequent causative agent for both sepsis and meningitis, about 28/60 and 7/12, respectively. These findings were very different with that reported in developed countries. In developed countries, Group B Streptococcus (GBS) is the major causative agent, followed by *Escherichia coli* (*E. coli*) and *Listeria monocytogenes*.[4,7,10,11] In Asia, namely Taiwan, also had GBS and *E. Coli* as the major cause for sepsis and meningitis in neonates.[5] Reports from poor and developing countries, like Nigeria and Ethiopia, showed Gram negative organisms, such as *E. coli*, *Klebsiella*, and *Enterobacter* were the top agents that cause neonatal meningitis.[12,13] In other developing countries, such as Panama and Haiti, although Gram negative organisms (*E. coli*, *Klebsiella*, *Enterobacter*, *Serratia*, and *Pseudomonas*) were still in the top charts for causing neonatal meningitis, the incidence of GBS infection tends to increase.[14,15] All studies above reported the same results, organisms that cause sepsis are almost identical with organisms that cause meningitis.

We found no GBS or *E. coli* in both blood and CSF culture. This was in accordance with previous findings by Rohsiswatmo,[16] in 2002, who reported *Enterobacter, Klebsiella,* and *Acinetobacter* as the three main organisms causing neonatal sepsis in Cipto Mangunkusumo Hospital. Rohsiswatmo[16] in her study also found no GBS. The absence of GBS infection maybe due to the absence or low rate of GBS vaginal colonisation in pregnant women at Cipto Mangunkusumo Hospital. Studies by Pohan[17] and Natadisastra[18] prove that GBS colonisation was very low in our population. Explanations for these differences were racial and geographical variations, widespread use of prophylactic broad spectrum antibiotics, and high nosocomial infections due to overcrowding and understaffing in neonatal units.[14]

Different patterns of antibiotics susceptibility from other studies can be predicted by difference patterns of organism causing neonatal meningitis. This pattern of antibiotic susceptibility will definetely influence the policy of empirical antibiotics therapy in the Perinatology Division at Cipto Mangunkusumo Hospital. Almost all organisms are resistant to first line antibiotics, except for chloramphenicol. Second line antibiotics which are still used is only ceftazidime (Table 3). In the special antibiotics group, imipenem and meropenem showed 100% sensitivity to all organisms causing neonatal meningitis (Table 4).

Classic first line antibiotics often used in developed countries, such as ampicillin, gentamicin, and cefotaxime were almost resistant to all organisms causing neonatal meningitis. Desinor *et al*,[15] also found organisms causing neonatal sepsis and meningitis which were highly resistant to ampicillin and gentamicin. A study by Rohsiswatmo *et al*,[16] also showed similar findings with gentamicin, ampicillin, and cefotaxime. As study in England and Wales by Heath and Holt,[4,10] on the contrary showed that gentamicin, ampicillin, and cefotaxime were still beneficial in treating neonatal sepsis and meningitis.

The differences between this study and other studies in developed countries are the pattern of organisms causing neonatal sepsis and meningitis. Prolonged use of third generation cephalosporins like cefotaxime was responsible for the rise incidence of Extended Spectrum Beta Lactamase (ESBL) producing Gram negative organisms infections.[19] These organisms can pro-

duce beta-lactamase which is highly resistant, not only to cephalosporins, but also to most aminoglycosides and many other antibiotics. Many of these ESBL were only sensitive to newer carbapenem antibiotics, such as imipenem and meropenem.[19]

The empirical antibiotic policy in all neonatology centers highly depends on the microorganism and its susceptibility pattern. Therefore, accuracy and continuity of data on microorganisms and antibiotics susceptibility in all neonatal units are highly important.[1, 2,19,20]

In conclusion, the prevalence of neonatal meningitis in Cipto Mangunkusumo Hospital in the year 2003-2004 was 18/60 neonates with bacterial sepsis. *Acinetobacter calcoaceticus* and other Gram negative bacteria are the major causes of neonatal meningitis in this hospital and are highly resistant to multiple antibiotics. Imipenem and meropenem have 100% sensitivity to all organisms found in this study.

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