Paediatrica Indonesiana

VOLUME 46 January - February • 2006 NUMBER 1-2

Original Article

Multidrug resistance in the neonatal unit and its therapeutic implications

Rinawati Rohsiswatmo

ABSTRACT

Background Neonatal septicemia constitutes an important cause of morbidity and mortality among neonates in Indonesia. The excessive use of antibiotics may cause antibiotic resistant bacteria and may cause neonatal fungal infection.

Objective To investigate the spectrum of organisms which cause neonatal sepsis and assess their sensitivity to various groups of drugs in the neonatal unit.

Methods A prospective study conducted on newborn babies delivered in Cipto Mangunkusumo Hospital, Jakarta from July 2004-May 2005 who presented clinical signs of septicemia were subjected for blood culture. Those sensitive to antibiotics for 7 days yet showed no clinical improvement were also cultured for fungi.

Results A total of 499 blood cultures were taken, 320 were positive for bacteria (positivity rate was 65.3%). There were 192 samples cultured for fungi, and the positivity rate was 64% (all for C*andida sp*). *Acinetobacter calcoaceticus* was the most common bacteria found (35.7%), followed by *Enterobacter sp* (7.0%), and *Staphylococcus sp* (6.8%). Most bacteria showed high degrees of resistance to commonly used antibiotics (ampicillin and gentamicin). There were also high degrees of resistance to cephalosporins by both Gram negative and Gram positive organisms. Only 61.7% of *A. calcoaceticus,* and 45.7% of *Enterobacter sp* were sensitive to ceftazidime. Gram negative organisms were also highly resistant to amikacin, but *Staphylococcus sp* was only moderately resistant. Resistance to carbapenem (meropenem and imipenem) varied from moderate to low. Drugs which were not used for newborn babies (quinolones/ciprofloxacin and chloramphenicol) varied from moderate to high resistance.

Conclusion Neonatal sepsis remains one of the major causes of mortality in our neonatal unit. Most organisms have developed multidrug resistance, and management of patients infected with these organisms and especially those with fungi infection are becoming a problem in developing countries **[Pediatr Indones 2006;46:25-31].**

Keywords: *multidrug resistance, neonatal sepsis*

Neonatal sepsis is one of the most common reasons for admission to neonatal units in developing countries.[1,2] In Cipto Mangunkusumo Hospital, Jakarta, more than 95% admissions to the unit are inborn, of whom 70% were unbooked deliveries. The annual number of admissions in Cipto Mangunkusumo Hospital is about 680 per year, sepsis accounts for almost 40% of the admissions. Neonatal sepsis is also a major cause of mortality in both developed and developing countries.[2,3] Gram negative organisms remain the major cause of neonatal sepsis in most developing countries.[1,4-10] During the 1960s, in Europe and America, Gram negative organisms were the most common cause of neonatal sepsis. This altered to group B streptococcus during the 1970s and coagulase-negative staphylococcus during the late 1980s and 1990s.[1,4-10] This is due to the changing pattern of antibiotic use and changes in lifestyle. The most disturbing thing was that these organisms have developed increasing multidrug resistance over the last two decades,[8,9-11] due to the indiscriminate and inappropriate use of antibiotics, over

From the Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Reprint requests to: Rinawati Rohsiswatmo, MD, Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Tel: 62-21-3144758/3154020.

the counter sale of antibiotics, lack of legislation to control their use, poor sanitation, and ineffective infection control in the maternity services.[12] Furthermore excessive antibiotic use causes neonatal fungal sepsis. Studies have consistently shown the duration of antibiotic use, particularly broad spectrum antibiotics, is the major risk factor for neonatal fungal infection.[13,14] The rapid emergence of multidrug resistant neonatal sepsis in developing countries is a new potential threat to the survival of newborn babies, who are often already in poor condition.

This study was done to investigate the spectrum of organisms which cause neonatal sepsis and assess their sensitivity to various groups of drugs in the neonatal unit.

Methods

This was a prospective study carried out in the Neonatal Unit at Cipto Mangunkusumo Hospital, Jakarta from July 2004-May 2005. Our unit performed routine blood cultures using the Bactec 9240 instrument (Becton Dickinson, USA) on all babies with clinical signs of septicemia. Babies who had received antibiotics before admissions were excluded.

Blood was taken by a standard method and cultured for bacteria in the Microbiology Clinical Pathology Laboratory at Cipto Mangunkusumo Hospital. Those sensitive to antibiotics for 7 days, but still showed no clinical improvement, were also cultured for fungi in the Parasitology laboratory at Cipto Mangunkusumo Hospital. Sensitivity to various antibiotics was tested by a standard disc diffusion technique, yet was not done to various antifungals due to limited budget.

Results

Blood culture results obtained from July 2004 to May 2005 was analysed. Out of 499 blood cultures, 320 were positive (positivity rate 65.26%); 178 (35.67%) were positive for *Acinetobacter calcoaceticus,* 35 (7.01%) for *Enterobacter sp*, 34 (6.81%) for *Staphylococcus sp,* 32 (6.41%) for *Klebsiella sp,* and 15 (3.01) for *Pseudomonas* (**Figure 1**). No group B streptococcus was grown from any culture. **Table 1**

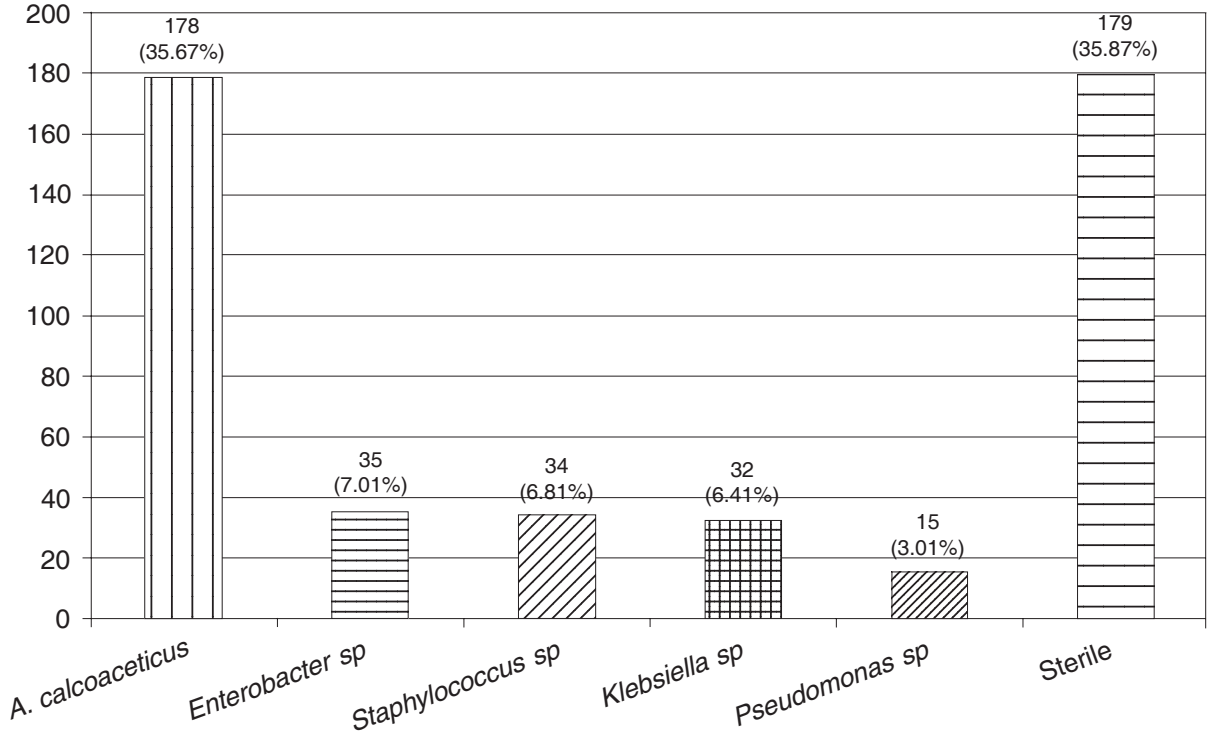

Figure 1. Five most common bacteria found in blood cultures at the Neonatology Division, Cipto Mangunkusumo Hospital during July 2004-May 2005

TABLE 1. NUMBER OF POSITIVE BLOOD CULTURES IN THE NEONATOLOGY DIVISION, CIPTO MANGUNKUSUMO HOSPITAL DURING JULY 2004-MAY 2005

Month	Number of subjects	Number of culture		Number of positive bacteria	%	Number of positive fungi	%
		Bacteria	Fungi				
July 2004	289	39	8	31	79.5	3	37.5
August 2004	204	41	15	21	51.2	13	86.6
September 2004	242	36	12	19	52.8	8	66.6
October 2004	243	26	3	21	80.1	1	33.3
November 2004	236	29	16	16	55.2	13	81.3
December 2004	211	20	12	11	55	9	75
January 2005	218	28	14	20	71.4	10	71.4
February 2005	218	44	15	27	61.4	13	86.6
March 2005	209	89	22	60	67.4	13	59.1
April 2005	298	105	38	56	53.3	20	55.2
May 2005	241	42	37	38	90.5	19	51.4
	2609	**499**	**192**	**320**	**65.26**	**122**	**64**

shows a total of 192 blood cultures for fungi, 122 were positive for *Candida sp* (positivity rate 64%).

The organisms' pattern of sensitivity was analysed for four groups of antibiotics:

1) Ampicillins and gentamicins are used as first line antibiotics;
2) cephalosporins, aminoglycosides, amoxicillin-clavulanic acid, and vancomycin are used as second line antibiotics;
3) cefepime, imipenem, and meropenem are used as a third line antibiotics;
4) quinolones and chloramphenicol are not recommended for use in children under 4 years of age, but may be indicated if the child has positive blood culture, severe sepsis, and if organisms are not sensitive to any other antibiotics.

Table 2 shows the pattern of sensitivity for *Acinetobacter calcoaceticus, Enterobacter sp*, *Staphylococcus sp, Klebsiella sp,* and *Pseudomonas* to various antibiotics. Gentamicin showed moderate response to *Enterobacter sp* and *Staphylococcus sp.* Most bacteria were resistant to cephalosporins except ceftazidime which remains to respond well to *Acinetobacter calcoaceticus, Enterobacter sp*, and *Pseudomonas sp.* Resistance to amikacin was also high in Gram negative organisms, but moderate to *Staphylococcus sp.* Resistance to carbapenem (meropenem and imipenem) varied from moderate to low. Drugs which were not used for newborn babies (quinolones/ciprofloxacin and chloramphenicol) showed a moderate to high resistance.

Discussion

About five million neonatal deaths occur worldwide each year, 98% of which occur in developing countries, particularly Asia and Africa. Infections such as tetanus, pneumonia, septicemia, meningitis, and diarrhea account for 30-50% of neonatal deaths in developing countries.[15] Neonatal sepsis is a life threatening emergency and any delay in treatment may result in death.

The spectrum of organisms which cause neonatal sepsis changes over time and varies from region to region. It can also vary from hospital to hospital in the same city. This is due to the changing pattern of antibiotic use and changes in lifestyle. The most common organisms which cause early and late onset sepsis in our study are very similar, which were Gram negative *Acinetobacter calcoaceticus, Enterobacter sp*, *Staphylococcus sp, Klebsiella sp,* and *Pseudomonas sp*. Siswanto *et al*,[16] from Harapan Kita Children's and Maternity Hospital, Jakarta; reported that *Serratia sp* is the leading

Table 2. Pattern of sensitivity to various antibiotics in the Neonatology Division, Cipto Mangunkusumo Hospital during July 2004-May 2005

	A.calcoaceticus	*Enterobacter sp*	*Staphylococcus sp*	*Klebsiella sp*	*Pseudomonas sp*
First Line					
Ampicillin	1.1%	5.7%	2.9%	0.0%	0.0%
Co-trimoxazole	**34.6%**	**37.1%**	23.5%	18.8%	**33.3%**
Gentamicin	5.3%	**37.1%**	**29.4%**	9.4%	20.0%
Kanamycin	7.0%	20.0%	11.7%	0.0%	20.0%
Erythromycin	0.0%	0.0%	8.8%	0.0%	0.0%
Oxacilin	0.5%	0.0%	14.7%	0.0%	0.0%
Second Line					
Amikacin	12.8%	**34.3%**	**44.1%**	**15.6%**	20.0%
Ceftazidime	**61.7%**	**45.7%**	17.6%	12.5%	**26.7%**
Amoxicillin - Clavulanic Acid	4.3%	20.0%	**29.4%**	6.3%	13.3%
Lincomycin	0.0%	0.0%	8.8%	0.0%	0.0%
Cefotaxime	2.7%	17.1%	17.6%	0.0%	0.0%
Ceftriaxone	2.6%	17.1%	17.6%	0.0%	0.0%
Vancomycin	1.6%		**29.4%**	0.0%	0.0%
Neomycin	0.0%	2.9%	0.0%	0.0%	0.0%
Aztreonam	1.1%	17.1%	0.0%	0.0%	0.0%
Third Line					
Cefepime	3.7%	**34.3%**	20.6%	21.9%	20.0%
Cefpirome	9.0%	22.9%	11.8%	0.0%	0.0%
Fosfomycin	0.0%	**48.6%**	2.9%	0.0%	0.0%
Meropenem	**77.7%**	**60.0%**	**29.4%**	**75.0%**	**40.0%**
Imipenem	**72.9%**	**60.0%**	**38.2%**	**75.0%**	26.7%
Fourth Line					
Chloramphenicol	**76.6%**	25.7%	**32.4%**	**31.3%**	**53.3%**
Ciprofloxacin	14.9%	**42.9%**	20.9%	**15.6%**	20.0%

cause of Gram negative sepsis. Suarca *et al*,[17] from Sanglah Hospital, Denpasar, Bali, found that *Enterobacter sp* are responsible for most cases**.** Joshi *et al*,[8] from India, reported Gram negative sepsis in 67.2% of their cases, with *Pseudomonas aeruginosa* being the most common organism (38.3%), followed by *Klebsiella* (30.4%) and *E. coli* (15.6%). Similar patterns have been reported in Trinidad and Southern Israel.[5,6]

Staphylococcus sp was the most common Gram positive organisms (6.8%) in our study. Similar results have been reported by Siswanto *et al,*[16] Jakarta. While Suarca[17] found coagulase-positive staphylococcus (25.0%) as the most common Gram positive bacteria, followed by coagulase-negative staphylococcus (9.6%).

Group B streptococcus was not isolated from any culture in our series. The same result has been reported in most of the studies from Indonesia, Pakistan, and other developing countries.[1-4,8,9,16,17] Ghiorgis[18] from Ethiopia did not find any group B streptococcus. On the other hand, in the series reported by Robbilard et *al,*[19] from Guadeloupe, group B streptococcus was grown from 46% of positive blood cultures, and 52% of gastric aspirates were positive for group B streptococcus. In Al Wasl Hospital, Dubai, Koutouby and Habib Ullah,[20] found 106 positive culture cases of neonatal sepsis with group B streptococcus being the most common organism (23%), particularly in early onset and late onset neonatal sepsis. Ohlsson *et al*[21] were the first to report the emergence of group B streptococcus in Saudi Arabia in the early 1980s.

The antimicrobial sensitivity pattern differs in different studies as well as at different times in the same hospital.[22-24] This is due to the emergence of resistant strains as a result of indiscrimate use of antibiotics. Indonesia has an enormous and growing problem of antibiotic use and abuse in newborn care. Simi-

lar problems of antibiotic resistance have been reported in many countries, including both industrialised countries (North America, Europe, and Australia) and in developing countries.[25-30] However, it seems that the situation is especially severe in Indonesia as it has reached the crisis level.

Our study showed a very high degree of resistance in Gram negative organisms to first line antibiotics (ampicillin), and 62.9%-94.7% resistance to gentamicin. About 97.1% of *Staphylococcus sp* were resistant to ampicillin. Suarca *et al*[17] from Denpasar, Bali, also reported the same result.

There was also a high degree of resistance to cephalosporins in both Gram negative and Gram positive organisms. Only 61.7% of *Acinetobacter calcoaceticus* and 45.7% of *Enterobacter sp* were sensitive to ceftazidime. Gram negative organisms were also highly resistant to amikacin, but *Staphylococcus sp* was only moderately resistant. The data of Anwer *et al*[1] from Karachi showed 80% resistance to ampicillin yet only 11-13% resistance to cefotaxime and 0-10% resistance to amikacin. Our study also showed that the resistance of *A. calcoaceticus, Enterobacter sp,* and *Klebsiella sp* to carbapenem, meropenem, and imipenem was low, yet the resistance of *Pseudomonas sp* (26.7%) and *Staphylococcus sp* (38.2%) was moderate. There was a high degree of resistance to quinolones, particularly ciprofloxacin. *Acinetobacter calcoaceticus* showed high sensitivity to chloramphenicol. Maryam *et al,*[9] from the Children's Hospital in Lahore reported that Gram positive *(Staphylococcus sp)* showed more resistance to quinolones yet Gram negative bacteria showed low resistance.

Emerging multiple drug resistance has also been reported in other parts of the world. Data of Orrett and Shurland[5] from Trinidad showed 85% of *S. aureus* are resistant to ampicillin, and *Pseudomonas* was 76.6% resistant to ceftazidime and 72.1% resistant to gentamicin. Joshi *et al*[8] from India showed a predominance of Gram negative bacteremia (67.2%) in their series, which had 25-75% resistance to cephalosporins, 68-78% resistant to piperacillin, and 23-69% resistant to gentamicin.

Friedman *et al*[11] from Toronto isolated ampicillin resistant *E. coli* from 75% of infants with early onset neonatal sepsis and 53% from a group with late onset neonatal sepsis. Gentamicin resistance was found in 50% if the early onset group and 16% of the late onset group. Kaushik *et al*[31] reported their bacterial isolates to be resistant to penicillin, ampicillin, and gentamicin, but had good sensitivity towards third generation cephalosporins and netilmicin. Leibovitz *et al*[32] reported the appearance of extremely virulent multiresistant *Klebsiella* in their neonatal intensive care unit at Kaplan Hospital, Israel. Kokasal *et al*[33] from India, reported a series of 35 cases of severe Gram negative neonatal sepsis, with all the organisms resistant to ampicillin, amoxillin, ticarcillin, cefazoline, cefotaxime, ceftazidime, ceftriaxone, and aminoglycoside. They treated these babies with meropenem and achieved 94.3% satisfactory clinical and bacterial response. The routine use of intrapartum antibiotic prophylaxis for the clinical prevention of group B streptococcus septicaemia in newborn babies has resulted in the appearance of ampicillin resistant Gram negative neonatal sepsis in a large number of developed countries.[34-36]

Infection by resistant organisms has been associated with treatment failure, higher morbidity and mortality, and increased costs. Furthermore, excessive antibiotic use causes neonatal fungal sepsis. Studies have consistently shown that the duration of antibiotic use, particularly broad spectrum antibiotics, is a major risk factor for neonatal fungal infection.[13,14] Neonatal fungal infection has almost exclusively been described in very low birth weight (VLBW) babies weighing <1500 grams at birth. In general, larger babies are almost never affected unless they require prolonged intravenous feeding and or prolonged intubation.

Our study showed 37.3% (122 in 327) neonates affected with fungal infection. About 60% neonates who had fungal infection were premature with birth weights <2000 grams. Rozaliyani's[7] study (2001-2003) in the Neonatology Unit at Cipto Mangunkusumo Hospital, reported a total of 52 neonates who had fungal infection, 61.5% were full term and 55.8% had birth weights >2500 grams. Since we had a budget limit, our study was unable to perform resistency and sensitivity tests for fungi. Rozaliyani *et al*[37] found a total of 135 neonates suspected of sepsis, 85 (62.96%) neonates had fungal infection. Of those who had fungal infection, only 52 neonates underwent sensitivity tests to various drugs. About 30.8% (16 out of 52) neonates had either bacteria or fungal infection. *Candida sp* were responsible for almost 80.9% of fungal infection episodes, with C.

tropicalis as the most common (48.5%) followed by *C. guilliermondii* (14.7%), *C. albicans* 11.8%, *C. glabrata* 4.46%, and *C. lusitaniae* 1.5%. *T. variabile* was also isolated for about 19.1%. Rozaliyani[37] also reported that *Candida sp* showed a higher degree of sensitivity to fluconazole compared to itraconazole.

Unless neonatologists stop using broad spectrum antibiotics for prolonged periods, resistance to antibiotics will rise. Resistance to the carbapenems, imipenem, and meropenem already appears in our unit, while various bacteria are resistant to all other antibiotics. Neonatologists must realize that overuse of broad spectrum antibiotics is irresponsible. The long-term results will be that neonatologists will have no antibiotics left to treat sepsis caused by certain organisms. Specialists in tertiary centers should discontinue using broad spectrum antibiotics for long periods of time and not accuse colleagues in district or private hospitals for misuse of antibiotics which should be selected for highly resistant organisms. All doctors must make a combined and concerned effort to improve prescribing practices.

There is a nine-point plan for antibiotic use. First of all, blood (and perhaps cerebrospinal fluid and/or urine) should always be taken before starting antibiotics. Second, the narrowest spectrum antibiotics possible is preferable, almost always penicillin (e.g. piperacillin-tazobactam) and an aminoglycoside (e.g. amikacin). Third, it is not advisable to use third generation cephalosporin (e.g. cefotaxim, ceftazidime) or a carbapenem (e.g. meropenem, imipenem). Fourth, the government should develop local and national antibiotic policies to restrict the use of expensive broad spectrum antibiotics like imipenem for emergency treatment. Fifth, the reliance on microbiology laboratory for blood culture results is advisable. Sixth, the raising C-reactive protein (CRP) does not always mean that the infant baby is definitely septic. Seventh, antibiotics can be stopped if blood culture result is negative within 2-3 days. Eighth, long periods of antibiotic use should be avoided. Ninth, nosocomial infection can be prevented by reinforcing infection control, specifically proper hand washing.

References

1. Anwer SK, Mustafa S, Pariyani S. Neonatal sepsis, an etiological study. J Pak Med Assoc 2000;59:91-4.
2. Dawadu A, Al-Umran K, Twum-Danso K. A case-control study of neonatal sepsis: Experience from Saudi Arabia. J Trop Pediatr 1997;43:84-8.
3. Stool BJ, Holman RC, Schuchat A. Decline in sepsis associated neonatal and infant deaths in the United States, 1979 through 1994. Pediatrics 1998;102:18.
4. Bhutta ZA, Yusuf K. Neonatal sepsis in Karachi, factors determining outcome and mortality. J Trop Pediatr 1997;43:65-70.
5. Orrett FA, Shurland SM. Neonatal sepsis and mortality in a regional hospital in Trinidad, aetiology and risk factors. Ann Trop Paediatr 2001;21:20-5.
6. Greenberg D, Shinwell ES, Yaguspsky P. A prospective study of neonatal sepsis and meningitis in southern Israel. Pediatr Infect Dis J 1997;16:768-73.
7. Ghiorghis B. Neonatal sepsis in Adis Ababa, Ethiopia, a review of 151 bacteremic neonates. Ethiop Med 1997;35:169-76.
8. Joshi SJ, Ghole VS, Niphadkor KB. Neonatal Gram negative bacteremia. Indian J Pediatr 2000;67:27-32.
9. Maryam W, Laeeg A, Maqbool S. Neonatal sepsis spectrum of antibiotic resistance. Proceedings of 10th National Annual Pediatric Conference;2001;p.57.
10. Kilani RA, Basamad M. Pattern of proven bacterial sepsis in neonatal intensive care unit in Riyadh Arabia, 2 year analysis. J Med Libon 2000;48:77-83.
11. Friedman S, Shah V, Ohisson A. Neonatal *Eschericha coli* infections: Concerns regarding resistance to current therapy. Acta Paediatr 2000;89:686-9.
12. Rahman S, Raghani MT, Ullah R. A survey of perinatal care facilities in Pakistan. Proceedings of 10th National Annual Pediatric Conference;2001;p.34.
13. Weese Mayer DE, Fondriest DW, Brouillette RT, S Hulman ST. Risk factors associated with candidemia in the neonatal intensive care unit, a case-control study. Pediatr Infect Dis J 1987;6:190-6.
14. Faix RG, Kovarik SM, Shaw TR, Johnson RV. Mucocutaneous and invasive candidiasis among very low birth weight (<1500 grams) infants in intensive care nurseries, a prospective study. Pediatrics 1989;83:101-7.
15. Darmstdt GL. Global newborn health challenges and opportunities. Proceedings of 10th a National Annual Pediatric Conference;2001;p.22.
16. Siswanto JE, Marnoto BW, Firmansyah R. The mortality rate of high risk infants with infection or septicemia in Harapan Kita Children and Maternity Hospital Jakarta [abstract]. In: Garna H, Nataprawira HMD, Alam A, editors. Proceedings

of the 13th National Child Health Congress; 2005 July 4-7; Bandung, Indonesia. Bandung; 2005. p. 301.

17. Suarca K, Kardana M, Iswari IS. Blood culture and sensitivity test pattern of early versus late onset sepsis in neonatal ward Sanglah Hospital Denpasar [abstract]. In: Garna H, Nataprawira HMD, Alam A, editors. Proceedings of the 13th National Child Health Congress; 2005 July 4-7, Bandung, Indonesia. Bandung; 2005. p. 110.
18. Ghiorghis B. Neonatal sepsis. Ethiop Med J 1991;28: 956-7.
19. Robbilard PY. Perez JM, Hulsey TC. Evaluation of neonatal sepsis screening in a tropical area, Part 1, major risk factors for bacterial carriage at birth in Guadeloupe. West Indian Med J 2000;49:312-5.
20. Koutouby A, Habib Ullah J. Neonatal sepsis in Dubai United Arab Emirates. J Trop Pediatr 1995;41:177-80.
21. Ohlsson A, Balley T, Takieddine F. Changing etiology and outcome of neonatal septicemia in Riyadh, Saudi Arabia. Acta Pediatr Scand 1986;75:540-4.
22. Freedam RM, Ingram DI, Gross I. A half century of neonatal sepsis at Yale. Am J Dis Child 1981;13:140-4.
23. Somu N, Shetty MV, Moses LG. A critical analysis of septicemia in infancy. Indian Pediatr 1976;13:443-6.
24. Bhakoo ON, Agarwal KC, Narang A. Prognosis and the treatment of neonatal septicemia a clinical bacterial study of 100 cases. Indian Pediatr 1974;11:519-28.
25. Gordon A, Isaacs D. Late onset infection and the role of antibiotic prescribing policies. Curr Opin Infect Dis 2004;17:231-6.
26. Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum betalactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, risk factors for induction and impact of resistance of outcomes. Clin Infect Dis 2001;32:1162-71.
27. Gupta A. Hospital acquired infections in the neonatal unit-*Klebsiella pneumoniae*. Semin Perinatol 2002; 27:340-5.
28. Royle J, Halasz S, Eagles G, Gilbert G, Dalton D. Jelfs P, *et al*. Outbreak of extended spectrum betalactamase-producing *Klebsiella pneumoniae* in a neonatal unit. Arch Dis Child Fetal Neonatal Ed 1999;80:64-8.
29. Pessoa-Silva CL, Meurer Moreira B, Camara Almeida V, Flannery B, Almeida Lins MC, Mello Sampaio JL, *et al*. Extended-spectrum betalactamase-producing *Klebsiella pneumoniae* in a neonatal intensive care unit, risk factors for infection and colonization. J Hosp Infect 2003;53:198-206.
30. Jain A, Roy I, Gupta MK, Kumar M, Agarwal SK. Prevalence of extended-spectrum betalactamase-producing Gram-negative bacteria in septicaemic neonates in a tertiary care hospital. J Med Microbiol 2003; 52:421-5.
31. Kaushik SL, Parmer VR, Grover N. Neonatal sepsis in Pakistan, presentation and pathogens. Acta Pediatr Scand 1991;80:596-601.
32. Leibovitz E, Flidel-Rimon O, Juster Reicher A. Sepsis in neonatal intensive care unit, a four year restrospective study (1989-1992). Isr J Med Sci 1997; 33:734-8.
33. Kokasal N, Hacimustafaoglu M, Bagei S. Meropenem in severe infections due to multiresistant Gram negative bacteria. Indian J Pediatr 2001;68:15-9.
34. Terrone DA, Rinehart BK, Eintein MH. Neonatal sepsis and death caused by resistant *Escherichia coli*, possible consequences of extended maternal ampicillin administration. Am J Obstet Gynecol 1999;180:1345-8.
35. Levin EM, Ghai V, Barton JJ. Intrapartum antibiotics prophylaxis increases the incidence of Gram negative neonatal sepsis. Infect Dis Obstet Gynecol 1999;7:210-3.
36. Mercer BM, Carr TL, Beazley DD. Antibiotic use in pregnancy and drug resistant infant sepsis. Am J Obstet Gynecol 1999;181:816-21.
37. Rozaliyani A. Profile of neonatal candidemia and resistency of *Candida sp* to azol derivates [thesis]. Jakarta: Parasitology Departement, Medical Faculty, Cipto Mangunkusumo Hospital, Univ. Indonesia; 2004.