JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Brief Original Article

Neonatal multidrug-resistant bacterial meningitis: a 29-year study from a tertiary hospital in Thailand

Anucha Thatrimontrichai[1], Waricha Janjindamai[1], Supaporn Dissaneevate[1], Gunlawadee Maneenil[1]

[1] Division of Neonatology, Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

Abstract

Introduction: This study aimed to compare the risks and case fatality rate (CFR) between neonatal multidrug-resistant (MDR) and non-MDR meningitis.

Methodology: a secondary analysis of a case-control studies in a Thai neonatal intensive care unit between 1990 and 2018 was performed. The pathogenic organisms causing neonatal meningitis were *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae*, *Acinetobacter* spp., and *Pseudomonas aeruginosa*. A MDR organism was defined as an isolate that was non-susceptible to at least 1 agent in at least 3 antimicrobial categories. The multivariate regression was analyzed for MDR and non-MDR samples of neonatal meningitis.

Results: Over a period of 29 years, the number of neonatal MDR and non-MDR meningitis cases were 17 and 21, respectively. The medians (interquartile ranges) of gestational age, birthweight and onset of meningitis were 35 (29.5-38) weeks, 1,945 (1,218-2,859) grams and 6.5 (2.8-17.9) days, respectively. The most common organism was *Acinetobacter baumannii* (32%). By multivariate analysis, neonates who had MDR meningitis were more likely to have a lower Apgar score at 5 minutes (adjusted odds ratio: 95% confidence intervals = 0.66 [0.44-0.99], p = 0.04). The crude CFR of neonatal meningitis was 32%. Non-survivors in MDR meningitis (58.8%) were significantly higher than non-MDR meningitis (9.5%, p = 0.004). The most common pathogen in non-survivors was carbapenem-resistant *Acinetobacter baumannii*.

Conclusions: Neonatal MDR meningitis has an association with lower APGAR scores, and higher CFR as well as *Acinetobacter baumannii*. Multifaceted infection prevention, and control programs for MDR organisms are crucial, and must be strictly implemented in high MDR areas.

Key words: *Acinetobacter baumannii*; carbapenems; meningitis; multi-drug resistance; neonatal sepsis.

J Infect Dev Ctries 2021; 15(7):1021-1026. doi:10.3855/jidc.12808

(Received 14 April 2020 – Accepted 12 November 2020)

Introduction

Neonatal meningitis is a life threatening disease, because of its high mortality (10-13%) [1-4] and morbidity (19.8 - 25.5%) [5,6]. From a systematic review, the incidence of neonatal meningitis in developing countries or resource-limited settings ranges was from 0.2 to 6.1 (Turkey 0.22, Costa Rica 0.25–2.66, Thailand 0.37, Africa and South Asia 0.81–6.1, Kuwait 2.4, Nigeria 4.7) cases per 1,000 live births, with a mortality rate between 40% and 58% [3,7-10]. Whereas in developed countries, the incidence is lower, with estimates around 0.2-0.3 per 1,000 live births, an overall mortality rate of 10% with 50% of cases having some form of disability at 5-year follow-up is observed [4,8,11]. Neonatal multidrug-resistant (MDR) sepsis and meningitis are a serious threat because of their high mortality and morbidity [8,10,12,13]. Incidence of multidrug-resistant (MDR) meningitis was 41%, and increased from 32% (1991-2002) to 58% (2003-2014); however, there was no statistically significant difference [10]. In Thailand, *Acinetobacter baumannii* meningitis was the most common (16%) causative organism as well as the cause of death in 40% of cases [10]. Nevertheless, there is limited research on neonatal MDR meningitis or carbapenem-resistant *Acinetobacter baumannii* (CRAB) pathogens.

We performed a secondary analysis in neonates who were admitted to the neonatal intensive care unit (NICU) at Songklanagarind Hospital, between 1990 and 2018. This study aimed to compare the risk of acquisition for MDR in comparison to non-MDR meningitis in a NICU.

Methodology

Setting and care practice

This study was conducted at the NICU, Songklanagarind Hospital, Songkhla, Thailand (15-bed, level IV, multi-bed, open ward in a university-affiliated teaching hospital), which is also the major tertiary care and referral center in southern Thailand.

There are approximately 3,000 live births at the hospital yearly, with about 500 inborn and transferred neonates admitted annually to the NICU. When meningitis is suspected, doses of empirical antimicrobial therapy for meningitis are started. Ampicillin plus gentamicin is administered for early onset meningitis (less than 72 hours), cefotaxime plus amikacin, carbapenems or colistin are used for late-onset meningitis (more than 72 hours). Further adjustments in the antimicrobial regimens and doses of meningitis therapy are based on antimicrobial susceptibility results or if the infant's clinical status does not improve within 48-72 hours. This is based on the judgment of the attending pediatrician or neonatologist.

Study design

The medical records of all admitted neonates in the NICU, as identified from the NICU's database and hospital's clinical microbiological laboratory database between 1 January 1990 and 31 December 2018, were included in the study. The inclusion criteria were all patients admitted to the NICU during the defined study period with the first episode of Gram positive (either *Staphylococcus aureus* or *Enterococcus* spp.) or Gram negative (either *Enterobacteriaceae* [all species], non-*Enterobacteriaceae* [*Pseudomonas aeruginosa* or *Acinetobacter* spp.]) organism in their cerebrospinal fluid (CSF) cultures [14]. Recorded data on patients included demographic parameters, antimicrobial susceptibility and outcome.

Definitions

A MDR organism was defined as: any isolate that was non-susceptible to at least one agent, in at least three antimicrobial categories [14]. Meningitis was only defined by any positive CSF culture. Bacteremia or ventilator-associated pneumonia (VAP) were defined by any positive blood or sputum culture having the same species and antibiograms before 7 days of positive CSF culture. VAP was diagnosed following the Centers for Disease Control and Prevention and National Healthcare Safety Network criteria for infants < 1 year old [15]. Congenital or acquired neurologic disease was defined as: spina bifida, meningoencephalocele or surgical neurological sequelae. Previous antibiotic exposure was defined as: intravenous antibiotic use for at least 72 hours before obtaining the culture.

Microbiological methods

Non-centrifuged CSFs were cultured by agar and broth techniques. CSF specimens were inoculated onto one 5% sheep blood plate and one chocolate agar plate and incubated at 35 °C in 5% carbon dioxide; these were then examined daily for 2 days. Additionally, the CSF specimens were inoculated into brain-heart infusion broth with V and X factors, and were incubated at 35 °C, then examined daily for 5 days. Blood cultures were processed in an automatic blood culture machine (BACTEC FX, Becton Dickinson, Franklin Lakes, NJ, USA or BACT/Alert, Organon Teknika Corporation, Durham, NC, USA). The isolated bacterial organisms were identified by standard laboratory methods. If bacterial growth was detected, a Gram stain was performed and the sample sub-cultured onto appropriate media and incubated overnight. Susceptibility testing was performed and interpreted by disk diffusion method, for each patient (zone diameter interpretive criteria), according to the most recently edited guidelines of the Clinical and Laboratory Standards Institute of the year of isolation [16].

Statistical analysis

The R program was used to develop a database of categorical and continuous variables. Categorical variables were analyzed as frequency and percentage, and compared using the χ^2 test or Fisher's exact test. Continuous (nonparametric) variables were analyzed as median (interquartile range [IQR]), and compared using the Mann-Whitney U-test. All p values were 2-tailed, with less than 0.05 indicating statistical significance. Univariate, multivariate, and collinearity (gestational age [GA] versus birthweight [BW] versus postmenstrual age [PMA], and Apgar score at 1 versus 5 minutes) analyzes were performed. Variables with $p < 0.2$ in univariate analysis, or variables that had a priori clinical significance (PMA, APGAR score at 5 minutes, bacteremia, and history of either the third generation of cephalosporin or aminoglycoside use) were entered into stepwise generalized linear regression models (glm) in multivariate analysis. The model with the lowest Akaike information criteria was judged as the most parsimonious model (Apgar score at 5 minutes, and history of the third generation of cephalosporin or aminoglycoside use). The adjusted odds ratio (OR) and 95% confidence intervals (CIs) were computed for variables independently associated with MDR versus non-MDR meningitis.

Results

Over a period of 29 years, the numbers of patient with meningitis were 52 neonates. Fourteen neonates were excluded: *Bacillus* sp. (n = 2), *Flavobacterium* sp. (n = 1), *Moraexella* sp. (n = 3), *Pseudomonas*

pseudoalcaligenes (n = 1), *Sphingobacterium* sp. (n = 1), *Staphylococcus epidermidis* (n = 2), *Streptococcus agalactiae* (n = 1), and *Streptococcus* not group B or D (n = 3). The number of neonatal MDR and non-MDR meningitis were 17 and 21 cases, respectively. The medians (IQRs) of GA, BW and onset of meningitis (postnatal age) were 35 (29.5-38) weeks, 1,945 (1,218-2,859) grams and 6.5 (2.8-17.9) days, respectively. The percentage of neonatal meningitis having an onset within 2, 3, and 7 days after birth were 4 (11%), 10 (26%) and 20 (53%) cases, respectively. The percentage of neonatal MDR meningitis during 2004-2018 (67%, 12/18) significantly increased, compared with those during 1990-2003 (25%, 5/20), $p = 0.02$. The pathogenic organisms causing neonatal meningitis (number of cases) were: *Acinetobacter baumannii* (n = 12), *Escherichia coli* (n = 8), *Klebsiella pneumonia* (n = 4), *Staphylococcus aureus* (n = 4), *Enterococcus* sp. (n = 3), *Proteus mirabilis* (n = 2), *Pseudomonas aeruginosa* (n = 2), *Serratia marcescens* (n = 1),

Table 1. Characteristics and risks of neonatal multidrug-resistant (MDR) and non-MDR meningitis.

Maternal and Neonatal characteristics	**MDR (n = 17)**	**Non-MDR (n = 21)**	***p*-value**
GA, weeks*	32.8 (5.4)	35.2 (4.2)	0.13
Preterm	11 (64.7)	10 (47.6)	0.47
BW, grams*	1,786.9 (866.2)	2,374.3 (1,138.6)	0.09
BW compared with GA			0.84
- appropriate for GA	12 (70.6)	16 (76.2)	
- small for GA	5 (29.4)	4 (19)	
- large for GA	0 (0)	1 (4.8)	
BW less than 1,500 grams	8 (47.1)	4 (19)	0.14
Male	8 (47.1)	9 (42.9)	1.00
Inborn	10 (58.8)	11 (52.4)	0.95
Born by cesarean section	7 (41.2)	8 (38.1)	1.00
Apgar score at 1 minute**	8 (6, 9)	9 (8, 9)	0.15
Apgar score at 5 minutes**	9 (7, 10)	10 (9, 10)	0.03
Antenatal steroid***	5/12 (41.7)	4/16 (25)	0.43
Antenatal antibiotic use***	1/13 (7.7)	2/12 (16.7)	0.59
Prolonged rupture of membrane > 18 hours***	2/13 (15.4)	1/11 (9.1)	1.00
Chorioamnionitis***	0/13 (0)	1/10 (10)	0.44
Risks at onset of disease	**MDR (n = 17)**	**Non-MDR (n = 21)**	***p*-value**
Postmenstrual age, weeks*	33.8 (5.7)	36.9 (3.9)	0.06
Postnatal age, days**	9.5 (3.6-15.5)	5.5 (2.7-26.7)	0.98
- within 48 hours	0 (0)	4 (19.0)	0.11
- within 72 hours	4 (23.5)	6 (28.6)	1.00
- within 7 days	8 (47.1)	12 (57.1)	0.77
Bacteremia	11 (64.7)	6 (28.6)	0.06
Ventilator-associated pneumonia	5 (29.4)	2 (9.5)	0.21
Congenital or acquired neurologic disease	3 (17.6)	5 (23.8)	0.71
Previous antimicrobial exposure	16 (94.1)	14 (66.7)	0.05
- ampicillin	10 (58.8)	10 (47.6)	0.72
- aminoglycoside	13 (76.5)	9 (42.9)	0.08
- 3rd cephalosporins	7 (41.2)	2 (9.5)	0.05
- carbapenems	3 (17.6)	1 (4.8)	0.31
Numbers of neonates with pathogenic organisms			0.01
- *Acinetobacter baumannii*	10 (58.8)	2 (9.5)	
- *Escherichia coli*	3 (17.6)	5 (23.8)	
- *Klebsiella pneumoniae*	1 (5.9)	3 (14.3)	
- *Staphylococcus aureus*	0 (0)	4 (19.0)	
- *Enterococcus* spp.	1 (5.9)	2 (9.5)	
- *Proteus mirabilis*	0 (0)	2 (9.5)	
- *Pseudomonas aeruginosa*	0 (0)	2 (9.5)	
- *Enterobacter cloacae*	1 (5.9)	0 (0)	
- *Klebsiella ozaenae*	1 (5.9)	0 (0)	
- *Serratia marcescens*	0 (0)	1 (4.8)	

Data are presented as number (%) unless indicated otherwise. * mean (standard deviation); ** median (interquartile range); *** missing data. Legend. GA: gestational age; BW: birth weight.

Enterobacter cloacae (n = 1) and *Klebsiella ozaenae* (n = 1). From antibiogram, two thirds (8/12) of *A. baumannii* were resistant to carbapenems (CRAB), whilst all *S. aureus* were susceptible to oxacillin. The crude CFR of neonatal meningitis was 32% (12/38). The pathogens in non-survivors were: *A. baumannii* (total = 7, only CRAB = 6), *Klebsiella* spp. (3) and *E. coli* (2).

Baseline characteristics were compared between MDR and non-MDR neonatal meningitis in Table 1. The percentage of neonatal MDR meningitis having an onset within 2, 3, and 7 days after birth were 0 (0), 4 (23.5), and 8 (47.1) cases, respectively. By univariate analysis, an APGAR score at 5 minutes and the type of pathogenic organisms had no statistically significant difference between the 2 groups. By multivariate analysis, neonates who had MDR meningitis were more likely to have a lower APGAR score at 5 minutes (crude OR: 95% CI = 0.71 [0.48-1.06]; adjusted OR: 95% CI = 0.66 [0.44-0.99]; *p* [Wald's test] = 0.04); whereas, history of either the third generation of cephalosporin (crude OR: 95% CI = 6.65 [1.16-38.20]; adjusted OR: 95% CI = 4.35 [0.60-31.25]; *p* [Wald's test] = 0.14) or aminoglycoside (crude OR: 95% CI = 4.33 [1.05-17.84]; adjusted OR: 95% CI = 3.63 [0.61-21.51]; *p* [Wald's test] = 0.16) use was not statistically significantly different. Moreover, non-survivors with MDR meningitis (10/17, 58.8%) were significantly higher than (crude OR: 95% CI = 13.57 [2.36-77.94]; *p* < 0.004) those with non-MDR meningitis (2/21, 9.5%).

Discussion

Some implications can be considered from our study. The choice of empirical antibiotics should be taken into account: local epidemiology, early versus late-onset of disease, patterns of resistance and availability within limited resource-settings. First, the pathogens within different regions and at specific times are differentially dominant organisms. In western countries, the major pathogens of neonatal meningitis are group B *Streptococcus* (GBS), *E. coli* and *Listeria monocytogenes* [17], whereas southeast Asia has the lowest amount of neonatal GBS diseases in the world [18,19], and neonatal listeriosis is uncommon [20]. In Thailand, *P. aeruginosa* was the most common pathogen causing neonatal meningitis between 1980-1990 [21]. Our study showed that *A. baumannii* as well as CRAB were the most common neonatal bacteremia, meningitis, VAP, and central line-associated bloodstream infections [10,22-28]. Second, a lower Apgar score was associated with MDR meningitis. Neuronal inflammation from birth asphyxia may increase bacterial penetration into the neurological system [29]. APGAR scores between MDR and non-MDR meningitis were statistically significant in difference but were not clinically significant in difference. Third, the cut-off point in "early versus late" onset of neonatal bacteremia and meningitis is still unclear, although usually within 72 hours after birth, with the exception of 7 days for GBS infection. Because the late onset of sepsis or meningitis is associated with healthcare associated infection, it usually requires broader spectrum antimicrobial therapy [8]. In this study, no neonate developed MDR meningitis within 48 hours of life but there was high prevalence of MDR meningitis, 23.5% and 47.1% after 72 hours and 7 days, respectively. Therefore, in high MDR and CFR areas the cut-off point should be considered as 48 hours, so as to avoid inadequate empirical antimicrobial therapy. Fourth, extremely broad-spectrum antibiotics (such as meropenem) are still inadequate empirical antimicrobial therapy, as both meropenem and colistin are considered off-label use in the neonatal period. In multivariate analysis, prompt antibiotic therapy with colistin significantly decreased the risk of mortality in neonatal MDR *A. baumannii* infection [30]. Colistin significantly increases penetration in CSF in pediatric meningitis; however, the concentrations may be inadequate for bacterial treatment [31]. Intraventricular colistin administration, due to *A. baumannii* cerebrospinal infection, is more effective than intravenous therapy alone. Recently, there have been a high percentage of colistin resistant *A. baumannii* isolates in Iraq (76%, 92/120) [32]. Therefore, more information is needed to determine long term safety and efficacy of colistin in neonates [33]. Finally, multifaceted infection prevention and control programs for MDR organisms are crucial, and should be strictly implemented in high MDR areas [34,35]. Antibiotic stewardship programs can significantly reduce the incidence of MDR *A. baumannii* infections and colonization, especially in Southeast Asia.

There are some limitations in our study. First, prevalence of MDR meningitis was under-reported, because not all organisms in the non-*Enterobacteriaceae* family were included. Only two species were identified and analyzed, because of the standardized international terminology by a group of experts from the US Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control [14]. Hence, other species needed a minimal inhibitory concentration to identify susceptibility testing. With this in mind, the greatest prevalence of non-*Enterobacteriaceae* pathogens, in

neonates, were due to *Acinetobacter* spp. and *P. aeruginosa* [10,25]. The under-reported cases may have occurred due to unstable clinical conditions from lumbar punctures, in addition underreporting might be linked to no routine postmortem diagnosis. Second, microbiological therapies (the second successive negative CSF cultures, after positive CSF culture) were not reported, because there was no routine, repeated lumbar puncture, unless the neonate had a persistent fever coupled with worsening clinical signs. Third, time of delayed administration of antimicrobials is lacking, due to the long duration of this retrospective study. Usage of antimicrobials may lead to MDR colonization and infection, but this study could not show the consumption of antimicrobial use in our unit. This resulted in incomplete long-term data, and lack of a standard definition of defined daily doses for neonates. Fourth, although the secondary data was collected for 29 years, there was only a small number of meningitis cases to analyze the exact risk of acquisition and mortality of neonatal MDR meningitis.

Conclusion

Neonatal MDR meningitis, especially CFR and CRAB organism, had a high prevalence within the recent periods (2004-2018). The cut-off point of neonatal sepsis should be considered as 48 hours, in high MDR areas. In the final model neonates with lower Apgar scores statistically increased the risk of MDR meningitis, although there was no significant clinical difference.

Acknowledgements

The authors thank the office of International Affairs, Prince of Songkla University, Thailand, for the English editing.

Authors' contributions

AT participated in the design of the study, performed the statistical analysis, drafted, reviewed and revised the manuscript. WJ, SD, and GM participated in its design and coordination, performed the initial analyses, and helped to draft the manuscript. All authors read and approved the final manuscript.

References

1. Gaschignard J, Levy C, Romain O, Cohen R, Bingen E, Aujard Y, Boileau P (2011) Neonatal bacterial meningitis 444 cases in 7 years. Pediatr Infect Dis J 30: 212-217.
2. Chang CJ, Chang WN, Huang LT, Huang SC, Chang YC, Hung PL, Tasi CY, Lu CH, Cheng BC, Lee PY, Chang HW (2003) Neonatal bacterial meningitis in southern Taiwan. Pediatr Neurol 29: 288-294.
3. Kavuncuoglu S, Gursoy S, Turel O, Aldemir EY, Hosaf E (2013) Neonatal bacterial meningitis in Turkey: epidemiology, risk factors, and prognosis. J Infect Dev Ctries 7: 73-81. doi: 10.3855/jidc.2652.
4. Holt DE, Halket S, de Louvois J, Harvey D (2001) Neonatal meningitis in England and Wales: 10 years on. Arch Dis Child Fetal Neonatal Ed 84: F85-89.
5. Stevens JP, Eames M, Kent A, Halket S, Holt D, Harvey D (2003) Long term outcome of neonatal meningitis. Arch Dis Child Fetal Neonatal Ed 88: F179-184.
6. Bedford H, de Louvois J, Halket S, Peckham C, Hurley R, Harvey D (2001) Meningitis in infancy in England and Wales: follow up at age 5 years. BMJ 323: 533-536.
7. Thaver D, Zaidi AK (2009) Burden of neonatal infections in developing countries: a review of evidence from community-based studies. Pediatr Infect Dis J 28 Suppl 1: S3-9.
8. Heath PT, Okike IO (2010) Neonatal bacterial meningitis: an update. Paediatr Child Health 20: 526-530.
9. Airede KI, Adeyemi O, Ibrahim T (2008) Neonatal bacterial meningitis and dexamethasone adjunctive usage in Nigeria. Niger J Clin Pract 11: 235-245.
10. Thatrimontrichai A, Kittivisuit S, Janjindamai W, Dissaneevate S, Maneenil G (2018) Trend and cut-off point of neonatal meningitis onset in a highly multidrug-resistant area. Southeast Asian J Trop Med Public Health 49: 438-446.
11. Hristeva L, Booy R, Bowler I, Wilkinson AR (1993) Prospective surveillance of neonatal meningitis. Arch Dis Child 69: 14-18.
12. Kumar M, Tripathi S, Kumar H, Singh SN (2018) Predictors of poor outcome in neonates with pyogenic meningitis in a level-three neonatal intensive care unit of developing country. J Trop Pediatr 64: 297-303.
13. Thatrimontrichai A, Premprat N, Janjindamai W, Dissaneevate S, Maneenil G (2020) Risk factors for 30-day mortality in neonatal Gram-negative bacilli sepsis. Am J Perinatol 37: 689-694.
14. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18: 268-281.
15. Centers for Disease Control and Prevention (CDC), National Healthcare Safety Network (NHSN) (2019) Pneumonia (ventilator-associated [VAP] and non-ventilator-associated pneumonia [PNEU]) event. Available: http://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf. Accessed: 31 January 2019.
16. Clinical and laboratory standard institute (CLSI) (2018) Performance standards for antimicrobial susceptibility testing, 28th edition. CLSI document M100-S28 (ISBN 1-56238-839-8).

17. Furyk JS, Swann O, Molyneux E (2011) Systematic review: neonatal meningitis in the developing world. Trop Med Int Health 16: 672-679.
18. Edmond KM, Kortsalioudaki C, Scott S, Schrag SJ, Zaidi AK, Cousens S, Heath PT (2012) Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet 379: 547-556.
19. Thatrimontrichai A, Khunnarakpong N, Tantichanthakarun P, Techato C, Nurak A, Sukumal R, Pasee S, Sujjanunt T, Rujeerapaiboon N (2017) Neonatal group B *Streptococcus* sepsis: a multicenter study in Thailand. Southeast Asian J Trop Med Public Health 48: 1063-1071.
20. Thatrimontrichai A, Khunnarakpong N, Techato C, Nakwan N, Nurak A, Sukumal R, Pasee S, Sujjanunt T, Rujeerapaiboon N, Prapruettrong A, Supabanpot S (2018) Neonatal Listeriosis with emphasis on Thailand, 1991-2016. Southeast Asian J Trop Med Public Health 49: 826-834.
21. Chotpitayasunondh T (1994) Bacterial meningitis in children: etiology and clinical features, an 11-year review of 618 cases. Southeast Asian J Trop Med Public Health 25: 107-115.
22. Thatrimontrichai A, Janjindamai W, Dissaneevate S, Maneenil G, Kritsaneepaiboon S (2019) Risk factors and outcomes of ventilator-associated pneumonia from a neonatal intensive care unit, Thailand. Southeast Asian J Trop Med Public Health 50: 537-545.
23. Thatrimontrichai A, Janjindamai W, Dissaneevate S, Maneenil G (2019) Factors and burdens of central line-associated bloodstream infections in a neonatal intensive care unit, Songkhla, Thailand. Southeast Asian J Trop Med Public Health 50: 742-749.
24. Thatrimontrichai A, Premprat N, Janjindamai W, Dissaneevate S, Maneenil G (2019) Multidrug-resistant Gram-negative bacilli sepsis from a neonatal intensive care unit: a case-case-control study. J Infect Dev Ctries 13: 603-611. doi: 10.3855/jidc.10402.
25. Thatrimontrichai A, Chanvitan P, Janjindamai W, Dissaneevate S, Jefferies A, Shah V (2014) Trends in neonatal sepsis in a neonatal intensive care unit in Thailand before and after construction of a new facility. Asian Biomed 8: 771-778.
26. Thatrimontrichai A, Techato C, Dissaneevate S, Janjindamai W, Maneenil G, Kritsaneepaiboon S, Tanaanantarak P (2016) Risk factors and outcomes of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia in the neonate: a case-case-control study. J Infect Chemother 22: 444-449.
27. Thatrimontrichai A, Rujeerapaiboon N, Janjindamai W, Dissaneevate S, Maneenil G, Kritsaneepaiboon S, Tanaanantarak P (2017) Outcomes and risk factors of ventilator-associated pneumonia in neonates. World J Pediatr 13: 328-334.
28. Thatrimontrichai A, Apisarnthanarak A, Chanvitan P, Janjindamai W, Dissaneevate S, Maneenil G (2013) Risk factors and outcomes of carbapenem-resistant *Acinetobacter baumannii* bacteremia in neonatal intensive care unit: a case-case-control study. Pediatr Infect Dis J 32: 140-145.
29. Barichello T, Fagundes GD, Generoso JS, Elias SG, Simoes LR, Teixeira AL (2013) Pathophysiology of neonatal acute bacterial meningitis. J Med Microbiol 62: 1781-1789.
30. Wei HM, Hsu YL, Lin HC, Hsieh TH, Yen TY, Lin HC, Su BH, Hwang KP (2015) Multidrug-resistant *Acinetobacter baumannii* infection among neonates in a neonatal intensive care unit at a medical center in central Taiwan. J Microbiol Immunol Infect 48: 531-539.
31. Antachopoulos C, Karvanen M, Iosifidis E, Jansson B, Plachouras D, Cars O, Roilides E (2010) Serum and cerebrospinal fluid levels of colistin in pediatric patients. Antimicrob Agents Chemother 54: 3985-3987.
32. Al-Kadmy IMS, Ibrahim SA, Al-Saryi N, Aziz SN, Besinis A, Hetta HF (2020) Prevalence of genes involved in colistin resistance in *Acinetobacter baumannii*: First report from Iraq. Microb Drug Resist 26: 616-622.
33. De Bonis P, Lofrese G, Scoppettuolo G, Spanu T, Cultrera R, Labonia M, Cavallo MA, Mangiola A, Anile C, Pompucci A (2016) Intraventricular versus intravenous colistin for the treatment of extensively drug resistant *Acinetobacter baumannii* meningitis. Eur J Neurol 23: 68-75.
34. Thatrimontrichai A, Apisarnthanarak A (2020) Active surveillance culture program in asymptomatic patients as a strategy to control multidrug-resistant gram-negative organisms: What should be considered? J Formos Med Assoc 119: 1581-1585.
35. Thatrimontrichai A, Pannaraj PS, Janjindamai W, Dissaneevate S, Maneenil G, Apisarnthanarak A (2020) Intervention to reduce carbapenem-resistant *Acinetobacter baumannii* in a neonatal intensive care unit. Infect Control Hosp Epidemiol 41: 710-715.

Corresponding author

Anucha Thatrimontrichai, MD.
Division of Neonatology, Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
Tel: +66 7445 1257
Fax: +66 7428 1251
Email: tanucha@medicine.psu.ac.th

Conflict of interests: No conflict of interests is declared.