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

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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.

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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 χ² 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)       | 0.14   |
| - small for GA                       | 5 (29.4)    | 4 (19)          | 0.15   |
| - large for GA                       | 0 (0)       | 1 (4.8)         |        |
| BW less than 1,500 grams             | 8 (47.1)    | 4 (19)          | 0.47   |
| 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)         | 0.47   |
| Apgar score at 5 minutes**           | 9 (7.10)    | 10 (9.1)        | 0.03   |
| Antenatal steroid***                 | 5/12 (41.7) | 4/16 (25)       | 0.43   |
| Antenatal antibiotic use***          | 1/3 (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      | MDR (n = 17) | Non-MDR (n = 21) | p-value |
| - 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 | MDR (n = 17) | Non-MDR (n = 21) | 0.01   |
| - Acinetobacter baumannii            | 10 (58.8)   | 2 (9.5)         | 0.01   |
| - Escherichia coli                   | 3 (17.6)    | 5 (23.8)        | 0.07   |
| - Klebsiella pneumonia               | 1 (5.9)     | 3 (14.3)        | 0.21   |
| - Staphylococcus aureus              | 0 (0)       | 4 (19.0)        | 0.72   |
| - Enterococcus spp.                  | 1 (5.9)     | 2 (9.5)         | 0.21   |
| - Proteus mirabilis                  | 0 (0)       | 2 (9.5)         | 0.21   |
| - Pseudomonas aeruginosa             | 0 (0)       | 2 (9.5)         | 0.21   |
| - Enterobacter cloacae               | 1 (5.9)     | 0 (0)           | 0.31   |
| - Klebsiella ozaeae                  | 1 (5.9)     | 0 (0)           | 0.31   |
| - 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 antibiotic, 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.

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**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.

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