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Risks and burdens of third-generation cephalosporin resistant *Enterobacteriaceae* in neonatal sepsis

Thatrimontrichai, A.[1*], Premprat, N.[1], Janjindamai, W.[1], Dissaneevate, S.[1] and Maneenil, G.[1]
[1]Division of Neonatology, Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand
[*]Corresponding author e-mail: tanucha@medicine.psu.ac.th
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Abstract. Third-generation cephalosporin resistant *Enterobacteriaceae* (TCRE) is a global concern especially in neonatal sepsis. We performed a secondary data analysis in a Thai neonatal intensive care unit to identify the risk factors for acquisition of TCRE sepsis and mortality of *Enterobacteriaceae* sepsis between 1991 and 2017. Multivariate logistic and Cox proportional regression were used for analysis. Numbers of neonates with TCRE and non-TCRE sepsis were 100 and 41 patients, respectively. Medians (interquartile ranges) of gestational age, birthweight, onset of sepsis and total hospital stay of neonates with *Enterobacteriaceae* sepsis were 32 (28, 38) weeks, 1670 (1025, 2750) grams, 11 (6, 25) days and 41 (22, 74) days, respectively. Univariate and multivariate analysis, neonates with TCRE sepsis were more likely to have birth asphyxia (adjusted odds ratio [aOR] = 2.6; 95% confidence interval [CI] 1.1-6.0; p = 0.02) and history of aminoglycoside exposure (aOR = 2.9; 95% CI 1.3-6.7; p = 0.01). In-hospital case fatality rate from *Enterobacteriaceae* sepsis was 26% (36/141). In Cox regression, neonates with TCRE sepsis was not an independent risk of non-survivors, but septic shock (adjusted hazard ratio = 9.9; 95% CI 5.0-19.7, $p < 0.001$) increased 30-day mortality in the final model. Asphyxia and previous aminoglycoside consumption were risks of acquisition for neonatal TCRE sepsis while the burden was not a significant difference. Infection prevention and control must be strictly implemented in high multidrug-resistant area.

INTRODUCTION

Neonatal sepsis is a worrisome concern especially multidrug-resistant pathogen. Trends of late onset Gram negative bacilli (GNB) bacteremia, especially due to the *Enterobacteriaceae* family, increased in a neonatal intensive care unit (NICU) (Thatrimontrichai *et al.*, 2014) and was associated with a higher case fatality rate (CFR) (Cohen-Wolkowiez *et al.*, 2009). Emergence of extended-spectrum beta-lactamase (ESBL) producing or third-generation cephalosporin resistant *Enterobacteriaceae* (TCRE) in neonatal sepsis is a concern due to the consideration of off-label use of meropenem and colistin in neonates (Simon & Tenenbaum, 2013; Thatrimontrichai *et al.*, 2013; Thatrimontrichai *et al.*, 2016).

However, antimicrobial-resistant bacteria may colonize from antibiotic selective pressure due to frequent and prolonged broad spectrum antimicrobial use. The emergence of multidrug-resistant GNB sepsis is particularly worrisome due to growing off-label use of antibiotics such as meropenem and colistin (Thatrimontrichai *et al.*, 2013). On the other hand, there are higher CFR in neonates who receive inadequate empiric antimicrobial therapy in high multidrug-resistant areas (Tsai *et al.*, 2014).

There are few reports on neonatal TCRE sepsis. Therefore, we aimed to clarify the risk factors for TCRE sepsis and mortality of neonatal *Enterobacteriaceae* sepsis in Thailand.

MATERIALS AND METHODS

Settings and Study Design

This study was conducted at the NICU of Songklanagarind Hospital, Songkhla, Thailand. The NICU is a 15-bed, multi-bed ward in a university-affiliated teaching hospital at Prince of Songkla University. There are approximately 2500–3500 live births with about 400–550 neonates admitted annually to the NICU.

This is a secondary analysis and retrospective study. Study subjects were identified from the hospital clinical microbiology laboratory database. All records were also reviewed to ensure that all eligible subjects were identified. Medical records of all neonates with *Enterobacteriaceae* sepsis obtained at any time during admission to the NICU from January 1, 1991 to December 31, 2017 were reviewed. TCRE and non-TCRE groups were neonates who had *Enterobacteriaceae* organisms from the cultures of blood or cerebrospinal fluid (CSF) or both. We performed surveillance for multidrug resistant (MDR) rates with attempts to identify any potential point source outbreak, if the MDR rates have been increased significantly. However, there was no evidence of outbreak during the entire study period.

Medical records from the medical record unit at Songklanagarind Hospital were reviewed. Recorded data of the patients included obstetric, intrapartum, and neonatal data such as patient demographic factors, devices used (i.e., ventilator or central line [CL]), antimicrobial use, antimicrobial susceptibility, and outcomes.

Definitions

Onset of sepsis was defined as the postnatal age developed signs of neonatal bacteremia or meningitis and obtained the culture. Birth asphyxia was defined as Apgar score less than 7 at 5 minutes of life. Neurologic disease was defined meningoencephalocele, spina bifida or surgical neurological sequelae. Cardiovascular disease was defined as congenital heart disease that is composed of acyanotic heart disease with signs of congestive heart failure and cyanotic heart disease. Gastrointestinal disease included esophageal atresia, pyloric stenosis, small or large bowel obstruction, omphalocele and gastroschisis.

Previous antimicrobial (third generation cephalosporins [cefotaxime or ceftazidime], cefoperazone-sulbactam, carbapenems [imipenem or meropenem] and aminoglycosides [gentamicin or amikacin]) exposure was defined as intravenous antibiotic use for at least 72 hours before obtaining the culture. CL was defined as an umbilical arterial/venous catheter or catheter by the cutdown technique. Device use and total parenteral nutrition were considered as risk factors if they occurred in the 7 days preceding the onset of sepsis. Criteria for the diagnosis of ventilator-associated pneumonia (VAP) and CL-associated bloodstream infection (CLABSI) followed the Centers for Disease Control and Prevention and National Healthcare Safety Network guidelines for infants < 1 year old (Thatrimontrichai *et al.*, 2019a; Thatrimontrichai *et al.*, 2019b).

Inadequate empirical antimicrobial therapy (IEAT) was defined as the use of antimicrobials more than 48 hours after the day that either blood or CSF culture were performed that did not cover the pathogens causing sepsis or administration of antimicrobials that failed to cover the resistant pathogens (Thatrimontrichai *et al.*, 2013). Patients were defined as having septic shock if they had sepsis plus hypotension (gestational age-dependent), persistent tachycardia or reduced peripheral perfusion evidence and needed vasopressor agents to maintain blood pressure within 48 hours after the onset of sepsis (Goldstein *et al.*, 2005). The 3-day, 7-day, 30-day, and in-hospital CFRs were calculated by dividing the number of deaths from sepsis by the number of individuals diagnosed with the sepsis on 3, 7 and 30 days after the onset of sepsis, and at discharge, respectively.

Microbiological Methods

All *Enterobacteriaceae* isolates were identified to the species level by standard laboratory methods. The isolates were cultured from blood and CSF. For blood

culture, a minimum of 1 mL of blood was incubated for five days at 35.5° or until there was a positive signal in the blood culture systems (BACTEC FX™). Positive culture was routinely performed using a blood agar plate (BAP), MacConkey agar, and chocolate agar. Non-centrifuged CSF was inoculated into Thioglycolate broth and cultured on BAP, MacConkey agar, and chocolate agar. The culture plates and broth were then incubated at 35°C with or without 5% carbon dioxide and examined daily for 2 and 10 days, respectively. The isolated organisms were identified by biochemical tests and the MLab system. Susceptibility testing was performed by Kirby-Bauer disc diffusion method on Muller-Hinton agar plates and interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines of the year of isolation (CLSI, 2018).

A TCRE organism was defined as *Enterobacteriaceae* that was non-susceptible to ceftriaxone, cefotaxime, ceftazidime and aztreonam but susceptible to tazobactam, cefoxitin, sulbactam and carbapenems, then others were incompatible with the above definition as non-TCRE organisms.

Statistical Analysis

R program was used to develop a database of categorical and continuous variables. Categorical variables are presented as frequency and percentage and were compared using the χ^2 test or Fisher's exact test. Non-parametric continuous variables were presented as median (interquartile range [IQR]) and compared using the Mann-Whitney U-test. All p values were two-tailed and P values less than 0.05 indicated statistical significance. We performed survival analysis by time-to-event (death within 30 days) after the onset of sepsis between TCRE and non-TCRE organisms.

Independent variables with $p < 0.2$ in the univariate analysis were retained for a regression model. The model with the lowest Akaike information criteria was judged as the most parsimonious model. Adjusted odds ratio (aOR) and hazard ratio (HR) with 95% confidence intervals (CI) were computed for variables independently associated with TCRE and non-TCRE groups by multivariate logistic regression model and nonsurvivors and survivors in *Enterobacteriaceae* sepsis by Cox proportional hazards model, respectively.

RESULTS

Between 1991 and 2017, the number of neonates with GNB and *Enterobacteriaceae* sepsis were 275 and 141 cases, respectively. The percentage of TCRE from *Enterobacteriaceae* sepsis was 71% (100/141). The percentages (neonates) of GNB, *Enterobacteriaceae* and TCRE sepsis in 10,341 neonates admitted to the NICU for the 27 years were 2.7% (275), 1.4% (141) and 1.0% (100), respectively. The prevalences (neonates) of GNB, *Enterobacteriaceae* and TCRE sepsis in 78,248 inborn neonates were 1.9 (152), 1.0 (79) and 0.7 (57) per 1,000 live births, respectively. Medians (IQRs) of gestational age, birth weight, onset of sepsis and total hospital stay of neonates with *Enterobacteriaceae* sepsis were 32 (28, 38) weeks, 1670 (1025, 2750) grams, 11 (6, 25) days and 41 (22, 74) days, respectively. There was no significant difference in onset of sepsis between TCRE and non-TCRE groups ($p > 0.05$). The number (percentage) of TCRE bacteremia was 97 (97) higher than 36 (88) non-TCRE bacteremia ($p < 0.05$). In-hospital CFRs from *Enterobacteriaceae* sepsis was 26% (36/141).

The results of univariate (Table 1) and multivariate (Table 2) analyses of the risk factors for acquisition in TCRE group was more likely to have birth asphyxia (aOR = 2.6; 95% CI 1.1-6.0) and exposure to aminoglycosides (aOR = 2.9; 95% CI 1.3-6.7) than non-TCRE group. Burden of neonatal TCRE sepsis compared with non-TCRE sepsis (excess CFR and duration during admission until discharge were 8% and 11 days) were not significantly different ($p > 0.05$ in Table 1).

By survival analysis, there was not statistically significantly difference in nonsurvivors between the TCRE and non-TCRE sepsis (HR = 1.6; 95% CI 0.7-3.8; p =

Table 1. Risk factors and burdens in neonates with third-generation cephalosporin resistant *Enterobacteriaceae* (TCRE) and non-TCRE sepsis

Risk factors	TCRE group (n = 100)	Non-TCRE group (n = 41)	*p*-value
GA (week), median (IQR)	32 (28, 37)	33 (30, 38)	0.25
BW (g), median (IQR)	1695 (1000, 2728)	1620 (1250, 2900)	0.30
BW compared to GA			0.42
Appropriate for GA	75 (75)	33 (81)	
Small for GA	24 (24)	7 (17)	
Large for GA	1 (1)	1 (2)	
Inborn	57 (57)	22 (54)	0.38
Vaginal delivery	46 (46)	22 (54)	0.52
Male	59 (59)	23 (56)	0.90
Birth asphyxia	52 (52)	11 (27)	< 0.001
Onset of sepsis (day), median (IQR)	14.2 (6.4, 26.2)	9.1 (3.5, 18.9)	0.07
Underlying disease before sepsis			
Neurologic disease	10 (10)	3 (7)	0.76
Cardiovascular disease	37 (37)	9 (22)	0.13
Gastrointestinal disease	14 (14)	9 (22)	0.36
Pulmonary hypertension	5 (5)	2 (5)	1.00
Previous antimicrobial exposure			
Third-generation cephalosporin	41 (41)	13 (32)	0.40
Cefoperazone-sulbactam	13 (13)	1 (2)	0.07
Carbapenems	15 (15)	4 (10)	0.58
Aminoglycosides	80 (80)	23 (56)	0.007
Ventilator use	64 (64)	22 (54)	0.34
Ventilator-associated pneumonia	7 (7)	1 (2.4)	0.44
CL use	41 (41)	11 (27)	0.16
CL-associated bloodstream infection	7 (7)	2 (5)	1.00
Total parenteral nutrition	55 (55)	21 (51)	0.82
Pathogenic organisms			0.003
Klebsiella spp.	64 (64)	16 (39)	
Escherichia coli	18 (18)	18 (43.9)	
Enterobacter spp.	18 (18)	6 (14.6)	
Serratia rubidaea	0 (0)	1 (2.4)	
Burdens	**TCRE group (n = 100)**	**Non-TCRE group (n = 41)**	***p*-value**
In-hospital CFR	28 (28)	8 (20)	0.40
3-day CFR	15 (15)	4 (10)	0.58
7-day CFR	18 (18)	4 (10)	0.33
30-day CFR	27 (27)	7 (17)	0.30
Length of stay (day), median (IQR)			
Admission until discharge	51 (26, 83)	40 (22, 63)	0.33
Onset of sepsis until discharge	23 (11 ,55)	23 (13, 46)	0.90

Data are presented as n **(%)** unless indicated otherwise.
BW indicates birth weight; CFR, case fatality rate; CL, central line; GA, gestational age.

Table 2. Univariate and multivariate analysis in neonates with third-generation cephalosporin resistant *Enterobacteriaceae* (TCRE) and non-TCRE sepsis

Risk factors	Crude odds ratios (95% confidence interval)	Adjusted odds ratios (95% confidence interval)	*p*-value (Wald test)
Birth asphyxia	3.0 (1.3, 6.5)	2.6 (1.1, 6.0)	0.02
Onset of sepsis	1.01 (0.99, 1.03)	0.99 (0.98, 1.02)	0.85
Cardiovascular disease	2.1 (0.9, 4.9)	1.4 (0.5, 3.5)	0.53
Previous cefoperazone-sulbactam use	6.0 (0.8, 47.3)	3.83 (0.4, 33.4)	0.22
Previous aminoglycosides use	3.1 (1.4, 6.9)	2.9 (1.3, 6.7)	0.01
Central line use	1.9 (0.9, 4.2)	1.7 (0.7, 4.0)	0.25

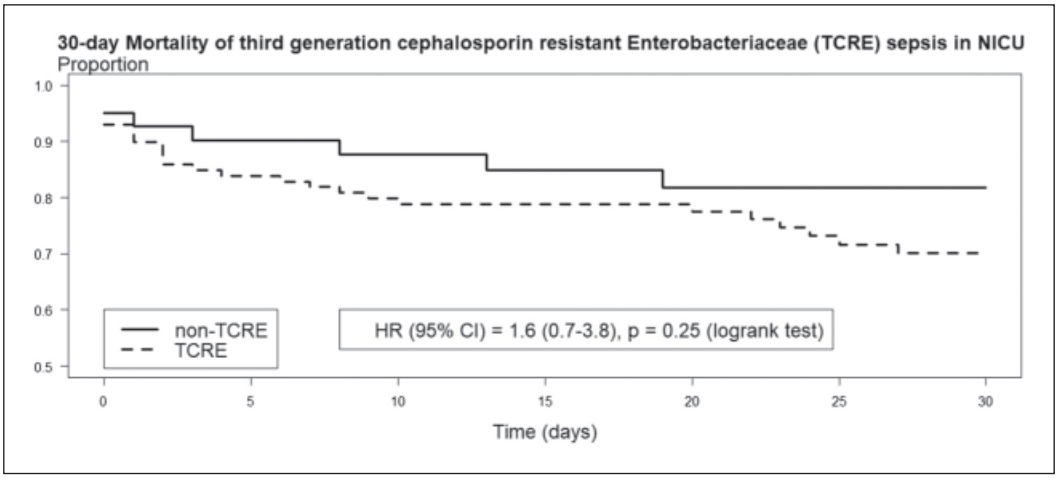

Figure 1. Thirty-day survival rate of neonates with third-generation cephalosporin resistant *Enterobacteriaceae* (TCRE) and non-TCRE sepsis.

0.25 by logrank test) in Fig. 1. By univariate analysis, risk factors of mortality (non-survivors) of *Enterobacteriaceae* sepsis were composed of weight at onset of sepsis, postmenstrual age, onset of sepsis more than 3 days, birth asphyxia, female and septic shock ($p < 0.05$) when compared with survivors. These variables and TRCE sepsis were put in the regression model then female and septic shock were retained in the final model. In Cox proportional hazards model, septic shock is an independent risk factor of nonsurvivors rather than survivors (adjusted HR = 9.9; 95% CI 5.0-19.7, $p < 0.001$), whereas for other risk factors including female and TCRE sepsis, there was no significant difference between nonsurvivors and survivors.

DISCUSSION

Birth asphyxia and previous aminoglycoside exposure of the neonate were associated with TCRE sepsis. However, TCRE sepsis was not a risk factor for mortality but septic shock was a key fatal factor in neonatal *Enterobacteriaceae* sepsis. Therefore, suspected neonatal sepsis with low Apgar score, previous aminoglycoside exposure and septic shock needs broad-spectrum empirical antimicrobial therapy until the second successive negative culture, especially in a high MDR area (Thatrimontrichai *et al.*, 2013; Thatrimontrichai *et al.*, 2016).

The prevalence of neonatal TCRE/*Enterobacteriaceae* sepsis (71%, 100/141) was similar to Senegal's study (79.7%, 55/69 neonates) (Breurec *et al.*, 2016). Neonates with risk factors for acquisition in TCRE group were more likely to have birth asphyxia and exposure to aminoglycosides than non-TCRE group. Whereas, the risk factor for infection and/or colonization with ESBL-producing bacteria in the NICU from meta-analysis showed birthweight, gestational age, Caesarean delivery, parenteral nutrition, length of stay in the NICU, mechanical ventilation, central venous catheter use, continuous positive airway pressure, endotracheal intubation, malformations, and previous antibiotic use (ampicillin/gentamicin, and cephalosporins) (Li *et al.*, 2017). Birth asphyxia may compromise immune defense then increase risk of neonatal infection and previous aminoglycoside consumption may be associated with MDR infection. Previous cephalosporin exposure was not a risk factor of neonatal TCRE sepsis, similar to pediatric ESBL-producing *Enterobacteriaceae* (ESBL-E) sepsis compared with non-ESBL-E sepsis in Thailand (Nivesvivat *et al.*, 2018).

The burden (CFR and length of hospital stay) in neonatal and pediatric drug resistant GNB sepsis is still unclear. The in-hospital CFR of *Enterobacteriaceae* sepsis in our study (25.5% [36/141]) was higher than in Taiwan (13.9% [50/360]) (Tsai *et al.*, 2016). The CFR in neonatal MDR GNB sepsis was higher than non-MDR GNB sepsis in Taiwan (Tsai *et al.*, 2014) (28.6% versus 10.5%, excess = 18.1%, $p < 0.05$) and Thailand (Thatrimontrichai *et al.*, 2019c) (37.6% versus 26.1%, excess = 11.5%). The CFR in ESBL-E sepsis was higher than non-ESBL-E sepsis in both Taiwan's neonates (Tsai *et al.*, 2016) (19.7% versus 12.5%, excess = 7.2%, $p > 0.05$) and Thailand's children (Nivesvivat *et al.*, 2018) (38.9% versus 13.3%, excess = 25.6%, $p < 0.05$). Excess CFR in our study was 8% and not significant between two groups ($p > 0.05$). While the length of hospitalization in neonatal MDR GNB (78.5 versus 75 days)(Tsai *et al.*, 2014), ESBL-E (71 versus 64 days) (Tsai *et al.*, 2016), and TCRE (51 versus 40 days) sepsis were not significantly different compared with non-resistant sepsis.

Risk factors for in-hospital mortality of neonatal ESBL-E sepsis were lower gestational age, birth weight and Apgar score, female, and several underlying chronic conditions (Tsai *et al.*, 2016) in the univariate analysis; similarly, our study showed lower weight at onset of sepsis, postmenstrual age and birth asphyxia, late onset of sepsis, female, and septic shock in TCRE group were higher than in non-TCRE group. In multivariate analysis, risk factors for in-hospital mortality of neonatal ESBL-E sepsis were small baby (lower gestational age and birth weight), secondary pulmonary hypertension and complications after bacteremia (Tsai *et al.*, 2016), whereas our study showed only septic shock increased risks for in-hospital mortality of neonatal TCRE sepsis.

This study has some limitations. First, the high prevalence of TCRE sepsis may result from referral bias as the referral center had a high volume of sick neonates and limited resources for infection prevention and control. Second, this study is a retrospective study so susceptibility test according to the most recently and annually edited guidelines of the CLSI were different in disc's zone for the long-time change. The susceptibility test was interpreted by E test and not performed by enzyme producer or serotype of pathogen. Therefore, TCRE sepsis, not ESBL-E sepsis, was defined in this study. Third, we lacked some data for risk factors (such as severity of illness at birth, maternal and neonatal colonization, and rate of antibiotic use in the unit) and sequalae (such as infectious and long-term complications). Final, there was not a significant difference of in-hospital CFR between TCRE and non-TCRE groups due to low power (15%) from post hoc analysis.

CONCLUSION

Neonatal risks of acquisition for TCRE sepsis were birth asphyxia and aminoglycoside consumption. Risk of mortality of neonatal *Enterobacteriaceae* sepsis was septic shock. Active surveillance culture program in asymptomatic neonates should be considered to inform the antibiotic stewardship program, and infection prevention and control (Thatrimontrichai & Apisarnthanarak, 2019).

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Ethical approval

The study was approved by the Ethical Committee Board of Faculty of Medicine, Prince of Songkla University (REC 58-263-01-1).

Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

REFERENCE

Breurec, S., Bouchiat, C., Sire, J.M., Moquet, O., Bercion, R., Cisse, M.F., Glaser, P., Ndiaye, O., Ka, S., Salord, H., Seck, A., Sy, H.S., Michel, R. & Garin, B. (2016). High third-generation cephalosporin resistant *Enterobacteriaceae* prevalence rate among neonatal infections in Dakar, Senegal. *BMC Infectious Diseases* **16**: 587.

CLSI. (2018). Performance Standards for Antimicrobial Susceptibility Testing. CLSI supplement M10024 Nov 2018 [cited 2018 24 Nov]: Available from: https://clsi.org/standards/products/microbiology/documents/m100/.

Cohen-Wolkowiez, M., Moran, C., Benjamin, D.K., Cotten, C.M., Clark, R.H., Benjamin, D.K., Jr. & Smith, P.B. (2009). Early and late onset sepsis in late preterm infants. *Pediatric Infectious Disease Journal* **28**: 1052-1056.

Goldstein, B., Giroir, B., Randolph, A. & International Consensus Conference on Pediatric Sepsis. (2005). International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatric Critical Care Medicine* **6**: 2-8.

Li, X., Xu, X., Yang, X., Luo, M., Liu, P., Su, K., Qing, Y., Chen, S., Qiu, J. & Li, Y. (2017). Risk factors for infection and/or colonisation with extended-spectrum beta-lactamase-producing bacteria in the neonatal intensive care unit: a meta-analysis. *International Journal of Antimicrobial Agents* **50**: 622-628.

Nivesvivat, T., Piyaraj, P., Thunyaharn, S., Watanaveeradej, V. & Suwanpakdee, D. (2018). Clinical epidemiology, risk factors and treatment outcomes of extended-spectrum beta-lactamase producing *Enterobacteriaceae* bacteremia among children in a Tertiary Care Hospital, Bangkok, Thailand. *BMC Research Notes* **11**: 624.

Simon, A. & Tenenbaum, T. (2013). Surveillance of multidrug-resistant Gram-negative pathogens in high-risk neonates – does it make a difference? *Pediatric Infectious Disease Journal* **32**: 407-409.

Thatrimontrichai, A. & Apisarnthanarak, A. (2019). Active surveillance culture program in asymptomatic patients as a strategy to control multidrug-resistant gram-negative organisms: What should be considered? *Journal of The Formosan Medical Association*. In press.

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. *Pediatric Infectious Disease Journal* **32**: 140-145.

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 Biomedicine* **8**: 771-778.

Thatrimontrichai, A., Janjindamai, W., Dissaneevate, S. & Maneenil, G. (2019a). Factors and burdens of central line-associated bloodstream infections in a neonatal intensive care unit, Songkhla, Thailand. *Southeast Asian Journal of Tropical Medicine and Public Health* **50**: 742-749.

Thatrimontrichai, A., Janjindamai, W., Dissaneevate, S., Maneenil, G. & Kritsaneepaiboon, S. (2019b). Risk factors and outcomes of ventilator-associated pneumonia from a neonatal intensive care unit, Thailand. *Southeast Asian Journal of Tropical Medicine and Public Health* **50**: 537-545.

Thatrimontrichai, A., Premprat, N., Janjindamai, W., Dissaneevate, S. & Maneenil, G. (2019c). Multidrug-resistant Gram-negative bacilli sepsis from a neonatal intensive care unit: a case-case-control study. *Journal of Infection in Developing Countries* **13**: 603-611.

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. *Journal of Infection and Chemotherapy* **22**: 444-449.

Tsai, M.H., Chu, S.M., Hsu, J.F., Lien, R., Huang, H.R., Chiang, M.C., Fu, R.H., Lee, C.W. & Huang, Y.C. (2014). Risk factors and outcomes for multidrug-resistant Gram-negative bacteremia in the NICU. *Pediatrics* **133**: e322-329.

Tsai, M.H., Lee, I.T., Chu, S.M., Lien, R., Huang, H.R., Chiang, M.C., Fu, R.H., Hsu, J.F. & Huang, Y.C. (2016). Clinical and molecular characteristics of neonatal extended-spectrum beta-lactamase-producing Gram-negative bacteremia: a 12-year case-control-control study of a referral center in Taiwan. *PLoS One* **11**: e0159744.