Review article:
NEONATAL SEPSIS IN THAILAND

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ABSTRACT

Neonatal sepsis is a burden around the world and causes high mortality and morbidity as well. Long-term neurodevelopmental disability may occur in survivors. General physicians, pediatricians, and neonatologists need be attentive to the proper diagnosis, starting, de-escalating or stopping empirical antimicrobials therapy in neonatal sepsis. Furthermore, multidrug resistant organisms have emerged among adults, children, and neonates in developing countries. Local epidemiology studies and antimicrobial stewardship programs are important for application of the best and specific treatments. Knowledge, definitions, and clinical practice of neonatal sepsis are updated in this review.

***Keywords**: Cross infections; neonatal sepsis; newborn; vertical infectious disease transmission*

ABSTRAK

Sepsis neonatal adalah salah satu permasalahan yang berat di seluruh dunia dan menyebabkan mortalitas dan morbiditas yang tinggi. Cacat perkembangan saraf jangka panjang dapat terjadi pada pasien yang dapat bertahan. Dokter umum, dokter anak, dan ahli neonatologi perlu memperhatikan diagnosis yang tepat, memulai, mengurangi atau menghentikan terapi antimikroba empiris pada sepsis neonatal. Lebih lanjut, organisme resisten multidrug telah muncul di antara orang dewasa, anak-anak, dan neonatus di negara berkembang. Studi epidemiologi lokal dan program penatagunaan antimikroba penting untuk penerapan perawatan terbaik dan spesifik. Pengetahuan, definisi, dan praktik klinis sepsis neonatal diperbarui dalam ulasan ini.

***Kata kunci**: infeksi silang; sepsis neonatorum; bayi baru lahir; transmisi penyakit menular vertikal*

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INTRODUCTION

Symptomatic neonatal sepsis is not difficult to diagnose and treat because physicians can perform a full septic work-up and start empirical antimicrobial therapy. However, treatment in asymptomatic neonates with a high risk of infection from the mother-baby dyad is still unclear. Nowadays, the definition and guideline of clinical chorioamnionitis have been up-dated.

Early onset and late onset neonatal sepsis (EOS and LOS) are different manifestations. Bacteremia and meningitis are common in EOS whereas device–associated infection (DAI), necrotizing enterocolitis (NEC), and fungal infection are common in LOS. Urinary tract infection is rare in EOS, except congenital anomalies of the kidney and the urinary tract, and there is a low incidence in LOS due to low urinary catheter utilization.

Definition and cut-off point of neonatal infection

Chorioamnionitis or intra-amniotic infection is associated with significant maternal, perinatal, and long-term adverse outcomes. “Intrauterine inflamma-tion or infection or both” abbreviated as “Triple I” is used instead of chorioamnionitis. The definitions and treatments of clinical chorioamnionitis (Polin & Com-mittee on Fetus and Newborn 2012) and suspected Triple I (Randis et al 2017, Higgins et al 2016) are presented in Table 1.

Commensal organisms should be carefully considered to be a contamination or pathogen. If the patient has clinical sepsis and commensal organisms from two or more blood specimens collected on separate occasions, the organisms should be considered pathogenic. National Healthcare Safety Network (NSHN) has updated common commensal organisms to include diphtheroids (Corynebacterium spp. not *C. diphtheria*), Bacillus spp. (not *B. anthracis*), Propionibacterium spp., coagulase-negative staphylococci (including *S. epidermidis*), viridans group streptococci, Aerococcus spp., Micrococcus spp., and Rhodococcus spp. (The Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) 2018).

The cut-off point of neonatal sepsis (EOS and LOS) is still ill-defined (eg 2, 3 or 7 days). Most definitions in the research field of EOS are defined as sepsis with an onset at 3 days of age or less (Polin & Committee on Fetus and Newborn 2012). However, developing countries are confronted with multidrug-resistant (MDR) infections including EOS (contamination during pregnancy and labor) and LOS (healthcare-associated infection). The cut-off point between EOS and LOS affects choice of empirical antimicrobial therapy. In Songklanagarind Hospital in southern Thailand from 1991 to 2016, the most common pathogen in LOS was Gram negative bacilli. The 10th and 50th percentiles of onset of MDR Gram negative bacilli (MDRGNB) sepsis were 2.2 and 8.9 days after birth, respectively. Accordingly, we suggest a cut-off point of 48 hours (10th percentile onset of MDRGNB sepsis) between EOS and LOS to be the appropriate time to start or step up to broad-spectrum antimicrobial therapy, especially in cases of septic shock or in a moribund neonate in a high MDR area (Thatrimontrichai et al 2016, Thatrimontrichai et al 2013).

Bacteremia

Causative organisms of EOS are group B Streptococcus (GBS) and *Escherichia coli*. Intrapartum antibiotic prophylaxis (IAP) has reduced the incidence of GBS infection in EOS and E. coli are now the dominant pathogens instead of GBS. In the USA, the incidences of pre- and post-IAP were 1.7 and 0.3 per 1,000 live births, respectively (Verani et al 2010). Southeast Asia reported the lowest incidence of GBS neonatal sepsis (Edmond et al 2012). In 13 hospitals and no routine IAP of Thailand, the incidence of GBS neonatal sepsis was 0.1 per 1,000 live births which was lower than post-IAP in the USA (Thatrimontrichai et al 2017a). The prevalence of maternal GBS colonization in Thailand was 12-18% and 11.3% in Songklanagarind Hospital. This prevalence was higher than India (2%), South Korea (6%), and Iran, and Turkey (9%), whereas it was lower than the USA (19-26%) (Thatrimontrichai et al 2017a). Moreover, listeriosis in neonates is rare in Thailand and has an intrinsic resistance to cephalosporin. The incidence of neonatal listeriosis from 15 hospitals showed 0.01 per 1,000 live births (Thatrimontrichai et al 2018a).

Table 1. Comparison of definitions and treatments in healthy-appearing or asymptomatic neonates between clinical chorioamnionitis and suspected Triple I

	Clinical chorioamnionitis	Suspected Triple I
Definition	1. Presence of maternal fever greater than 38°C and 2. At least 2 of the following criteria: 2.1 Maternal leukocytosis (greater than 15,000 cells/mm^3) 2.2 Maternal tachycardia (greater than 100 beats/minute) 2.3 Fetal tachycardia (greater than 160 beats/minute), 2.4 Uterine tenderness 2.5 Foul odor of the amniotic fluid.	1. Maternal oral temperature 39.0°C or greater on any one occasion without a clear source (if the oral temperature is 38.0-39.0°C, repeat the measurement in 30 minutes; if the repeat value remains at least 38.0°C, it is documented fever) 2. Any of the following: 2.1 Baseline fetal tachycardia (greater than 160 beats per min for 10 min or longer, excluding accelerations, decelerations, and periods of marked variability) 2.2 Maternal white blood cell count greater than 15,000 per mm^3 in the absence of corticosteroids 2.3 Definite purulent fluid from the cervical os
Treatment	- requiring antimicrobial agents soon after birth and independent on gestational age (GA) and results of initial complete blood count (CBC) and C-reactive protein (CRP)	- GA less than 35 weeks: work-up (CBC and CRP) and empirical antimicrobial prophylaxis - GA 35 weeks or greater: observe and re-evaluate (closely monitor within 6 hours and observe until 48 hours of life)

Causative gram-positive and negative organisms of LOS are coagulase negative Staphylococcus (CoNS), *Staphylococcus aureus*, Klebsiella species, and Acinetobacter species (Thatrimontrichai et al 2014). Prolonged device use (endotracheal intubation and central line) and the environment in a neonatal intensive care unit (NICU) are the main resources of infection as well as preterm neonates (Thatrimontrichai 2014a).

In Songklanagarind Hospital between 1991 and 2016, the top 4 MDRGNB organisms were *Klebsiella pneumoniae* (83 episodes), *Acinetobacter baumannii* (57 episodes), *E. coli* (28 episodes), and *Enterobacter cloacae* (28 episodes). The top 3 non-MDRGNB organisms were *A. baumannii* (38 episodes), *Pseudomonas aeruginosa* (22 episodes), and *E. coli* (17 episodes). The incidences of GNB and MDRGNB sepsis in inborn neonates were 1.8 and 1.2 per 1000 live births, respectively. The case fatality rates in the GNB and MDRGNB sepsis groups were 33.5% (82/245) and 37.6% (59/157), respectively.

Meningitis

The causative organisms of neonatal meningitis in the USA and Thailand (Queen Sirikit National Institute of Child Health and Songklanagarind Hospital) were GBS, Pseudomonas species and *A. baumannii*, respectively (Thatrimontrichai et al 2018b). Combination (ampicillin plus gentamicin or cephalosporin plus amikacin) and broad-spectrum (cefoperazone-sulbactam or carbapenems) empirical antimicrobial therapy may not cover the extensively drug-resistant pathogens (eg, carbapenem-resistant *A. baumannii* [CRAB]). Unfortunately, CRAB is the most common causative organism in neonatal meningitis in Songklanagarind Hospital. Intrathecal colistin injection is not recommended in CRAB meningitis. *Listeria meningitis* is a rare organism and has never been reported in Thailand.

DAI

DAI including ventilator–associated pneumonia (VAP) and central line–associated bloodstream infection (CLABSI) is worrisome in the NICU. Device bundle care reduces and prevents DAI. Early extubation and non-invasive ventilation, and off-central line if not necessary are the keys of bundle care. The maximum duration of umbilical arterial or venous catheters are recommended up to 5 days or 14 days, whereas peripherally inserted central catheter depends on the manufacturer recommendations, for example Vygon™ suggests up to 28 days.

A neonatal birthweight less than 750 grams and sedative medication use were independent risk factors for VAP (Thatrimontrichai et al 2017b). In Songklanagarind Hospital from 2014 to 2016, the standardized infection ratio (SIR) of VAP was higher than in the USA (5.5 times compared with NSHN) but lower than developing countries (0.5 times compared with International Nosocomial Infection Control Consortium [INICC]) (Table 2). Moreover, SIR due to CLABSI was higher than in the USA (2.8 times compared with NSHN) but lower than developing countries (0.2 times compared with INICC) (Table 3).

NEC

NEC is an emergency of gastrointestinal disease in neonates and difficult to diagnosis due to subjective criteria. NEC may be under-diagnosed or overdiagnosed from clinical and radiographic criteria because the criteria depend on the experience of the physicians (Thatrimontrichai 2014b). There are poor complications if under-diagnosed (development of advanced severity, short bowel syndrome, and intestinal failure) and if over-diagnosed (long-term parenteral nutrition, antimicrobial therapy, and central line utilization).

In Songklanagarind Hospital from 2010 to 2016, the incidence of NEC in very low birthweight (VLBW) infants was 15% (65/444). Transfusion-associated NEC (TANEC) was defined as NEC that develops within 48 hours of a red blood cell transfusion. The percentage of TANEC from the total number of NEC and numbers of blood transfusion were 14% (9/65) and 0.8% (9/1190), respectively.

Patients born preterm is a risk factor, whereas breastmilk is a protective factor in NEC (Thatrimontrichai 2017). Breastmilk reduced the complications of preterm infant (severe retinopathy of prematurity and bronchopulmonary dysplasia) (Bharwani et al 2016, Villamor-Martinez et al 2018). Probiotics and lactoferrin were able to reduce the incidence of NEC as well in low-income and medium-income countries (He et al 2018, Deshpande et al 2017); however, there is a need for more information on the clinical implications in routine care. Gut microbiota is a new research field to improve preterm neonates who develop NEC (Thatrimontrichai 2017).

Table 2. Incidence density of ventilator-associated pneumonia (VAP), ventilator utilization ratio (VUR), and standardized infection ratio (SIR) from 2014 to 2016 compared with NSHN (2013) and INICC (2010-2015)

Birthweight (grams)	VAP/1000 ventilator-days	VUR (ventilator-days/patient-days)	SIR* (NSHN)	SIR* (INICC)
≤750	6.13 (5/815)	0.46 (815/1765)	5.9	1.3
751-1000	2.04 (1/491)	0.36 (491/1370)	1.8	0.3
1001-1500	0 (0/410)	0.33 (410/1235)	0	0
1501-2500	4.77 (4/839)	0.48 (839/1740)	8.8	0.3
>2500	5.58 (7/1255)	0.62 (1255/2035)	38.9	0.5
Total	4.46 (17/3810)	0.47 (3810/8145)	5.5	0.5

INICC: International Nosocomial Infection Control Consortium, NSHN: National Healthcare Safety Network, SIR; standardized infection ratio.
*SIR: (number of VAP in this study x 1000)/(pooled mean VAP from standard paper x ventilator-days in this study)

Table 3. Incidence density of central line-associated bloodstream infection (CLABSI), central line utilization ratio (CUR), and standardized infection ratio (SIR) from 2014 to 2016 compared with NSHN (2013) and INICC (2010-2015)

Birth weight (grams)	CLABSI/1000 central line-days	CUR (central line-days/patient-days)	SIR* (NSHN, 2013)	SIR* (INICC, 2010-2015)
≤750	8.11 (6/740)	0.43 (740/1,733)	3.9	0.4
751-1000	0 (0/590)	0.43 (590/1,370)	0	0
1001-1500	0 (0/591)	0.54 (591/1,087)	0	0
1501-2500	4.22 (4/947)	0.62 (947/1,518)	7.5	0.2
>2500	2.46 (3/1,220)	0.69 (1,220/1,776)	3.3	0.2
Total	3.18 (13/4,088)	0.55 (4,088/7,484)	2.8	0.2

INICC: International Nosocomial Infection Control Consortium, NSHN: National Healthcare Safety Network, SIR; standardized infection ratio.
*SIR: (number of CLABSI in this study x 1000)/(pooled mean CLABSI from standard paper x central line-days in this study)

Invasive fungal infection (IFI)

The case fatality rate in neonatal IFI is higher than in Gram negative or Gram positive infections. The risk factor of IFI is prematurity. In a meta-analysis, oral/ topical and systemic antifungal prophylaxis in VLBW infants reduced IFI compared with control groups (relative risk (RR) = 0.20, 95% confidence interval (CI) 0.14-0.27 and RR = 0.43, 95% CI 0.31-0.59, respectively) (Austin et al 2015, Cleminson et al 2015).

Although there is a strong benefit from antifungal prophylaxis in VLBW, antifungal prophylaxis is not practiced routinely in Songklanagarind Hospital. The incidence of IFI in VLBW infants from 2005 to 2016 was 2.6% (27/1,027) and lower than the therapeutic group for oral/topical (4.4%, 40/904) and systemic (6.3%, 47/752) administrations. Outborn neonate, history of cefoperazone plus sulbactam use, invasive mechanical ventilation, and total parenteral nutrition were the significant risk factors of IFI. The case fatality rates of IFI in all neonates and VLBW neonates were 31.3% and 33.3%, respectively.

CONCLUSION

Neonatal sepsis is a serious problem and still challenges both clinicians and researchers. Sophisticated neonatal care improves survival in preterm infants; however, they need long-term device use, antimicrobial exposure, and long hospital stay. Sepsis does not decrease but MDR organisms emerge and are persistent global health threats (Chusri & Tuanyok 2018). Local epidemiology studies and antibiotic stewardship programs are needed for application in clinical practice.

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