

## REVIEW

# NEONATAL LISTERIOSIS WITH EMPHASIS ON THAILAND, 1991-2016

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**Abstract.** In Thailand, the current prevalence of neonatal listeriosis is unclear. From a review of medical records of neonates from 11 neonatal care units in Thailand during 1991-2016, eight patients (7 inborn, one transferred) were identified as having *Listeria monocytogenes* sepsis, resulting in a prevalence of neonatal listeriosis of 0.18/10,000 live births and a case fatality rate of 12%. Thus, in Thailand neonatal listeriosis is rare and with a lower case-fatality rate than reported in other countries.

**Keywords:** *Listeria monocytogenes*, bacteremia, listeriosis, neonatal sepsis, newborn

## INTRODUCTION

Listeriosis is a food- and blood-borne disease caused by *Listeria monocytogenes*, an opportunistic intracellular gram-positive bacillus, which targets cells of the monocyte-macrophage lineage (Isaacs, 2014). Humans can become infected by

ingestion of contaminated food, such as undercooked chicken, unwashed vegetables, unpasteurized dairy products and poorly refrigerated food items (Jacobson, 2008; Isaacs, 2014).

Listeriosis is a rare but severe disease with low morbidity and high mortality. Pregnant women, fetuses and neonates are among the high-risk populations, with 12-20 times the prevalence of listeriosis than the normal population (Jacobson, 2008; Elinav *et al*, 2014). In cases of congenital listeriosis, a neonate may present with embolic and granulomatous rash (granulomatosis infantiseptica) (Jacobson, 2008; McKinney, 2016) and hepatospleno-

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megaly, indicating transplacental or hematogenous transmission. Listeriosis can also be diagnosed by a presence of macro abscesses in the placenta (Topalovski *et al*, 1993). Clinical manifestations of congenital listeriosis include meconium-stained amniotic fluid with preterm labor, rash, hepatosplenomegaly, severe respiratory distress, meconium aspiration syndrome (MAS) and persistent pulmonary hypertension of the newborn (PPHN) following MAS (Becroft *et al*, 1971; Halliday and Hirata, 1979).

*L. monocytogenes* causes both early- (EOL) and late-onset neonatal listeriosis (LOL), which can lead to bacteremia and meningitis. Previous studies found EOL is more common (70%), manifesting in bacteremia and premature birth, while most LOL cases manifested as meningitis (McLauchlin, 1990; Gellin *et al*, 1991). Healthcare-associated infections may arise from contaminated medical instruments or products, such as mineral oil (Schuchat *et al*, 1991), rectal thermometer (Larsson *et al*, 1978) and stethoscopes (Fullerton *et al*, 2015). Recent reported prevalence rates of congenital listeriosis range from 0.03% (4/11,795) in China during 2013 (Lv *et al*, 2014) and 0.08% (1/1,192) during 2006-2010 in the USA (Hassoun *et al*, 2014). In Thailand, *Listeria*-associated bacteremia and meningitis in neonates are rare (Thatrimontrichai *et al*, 2014; *ibid*, 2018).

The current mainstay treatment of listeriosis is ampicillin plus an aminoglycoside (Jacobson, 2008), although clinical reports suggest penicillin G is probably just as effective as ampicillin (Isaacs, 2014). As the intracellular life-cycle of *Listeria* provides protection from host innate and adaptive immune responses, effective antibiotic treatment requires agents able to penetrate, distribute, and remain stable

within host cells. Prolonged use of high-dose ampicillin significantly improves neonatal outcome (Lamont *et al*, 2011). Monotherapy involving third generation cephalosporins or gentamicin treatment is contraindicated because *Listeria* is inherently resistant to cephalosporins and gentamicin has very poor penetration into intracellular spaces (Traub, 1981; McKinney, 2016).

In Thailand, the current prevalence of neonatal listeriosis is unclear because there is no mandatory reporting system. Hence, this study was undertaken to identify prevalence and case fatality rate (CFR) of listeriosis in neonatal care units in Thailand.

## MATERIALS AND METHODS

### Subjects and study design

This study examined records from 11 hospitals (two university hospitals, four tertiary level hospitals, three secondary level hospitals, and two primary level hospitals) in Thailand, namely, Hat Yai, Songklanagarind, and Songkhla Hospitals in Songkhla Province; Burapha University Hospital in Chonburi Province; Nakhon Pathom Hospital in Nakhon Pathom Province; Thasala and Thung Song Hospitals in Nakhon Si Thammarat Province; Vachira Phuket Hospital in Phuket Province; Phatthalung Hospital in Phatthalung Province; Trang Hospital in Trang Province; and Kuankalong Hospital in Satun Province. Subjects were identified by retrospective reviewing the hospitals' medical, and microbiology and laboratory records. All patients <28 days of age with a diagnosis of listeriosis admitted from 1 January 1991 to 31 December 2016 with available medical records were included in the study. Although each hospital had different periods for which the required records

were available, data were collected from medical records completed within the study period.

Infants with listeriosis were those who had a history of positive blood or cerebrospinal fluid (CSF) culture for *L. monocytogenes* identified based on routine laboratory standards at the study hospital. The onset of sepsis was defined as the time at which a culture positive for *L. monocytogenes* was obtained. Although there are different definitions for EOL and LOL (Table 1), this study defines EOL and LOL as onset of sepsis <3 days and ≥3 days, respectively.

## RESULTS

During the study period (26 years) there were eight neonates with blood and

culture confirmed listeriosis (Table 2). It is worth noting that during the first 12 years of the survey (1991-2012), there were no cases of neonatal and all eight cases were from the period 2013-2016. Seven were born at one of the study hospitals (inborn) and one had been transferred to a study hospital (transferred). Seven neonates had EOL and one LOL. An overall incidence of listeriosis among inborn neonates was 0.18/10,000 live births (7/385,612 live births) over the period 1991-2016. The incidence of listeriosis among inborn neonates during the period 2013-2016 was 0.45/10,000 live births (7/157,091 live births) and of EOL (inborn) was 0.38/10,000 live births (6/157,191 live births). In terms of seasonal incidence of listeriosis, the highest incidence rates were in March and November (Table 2).

Table 1  
Incidence and case-fatality rate (CFR) of neonatal listeriosis.

Country, study period (reference)	Incidence (per 10,000 births)	CFR		
		EOL	LOL	Total
Algeria, 2000 (Ramdani-Bouguessa and Rahal, 2000)	-	50% (1/2)*	-	50% (1/2)
Australia, 1978-1979 (Niels le Souef and Walters, 1981)	-	(-/11)	(-/1)	17% (2/12)
Australia, 1983-1994 (Craig <i>et al</i> , 1996)	2.0	-	-	14% (2/14)
Canada, 1981 (Evans <i>et al</i> , 1985)	-	-	-	47% (7/15)
Canada, 1999 (Banerji and Noya, 1999)	-	0% (0/1)	-	0% (0/1)
China, 1964-2010 (Feng <i>et al</i> , 2013)	-	-	-	46% (21/46)
China, 2008 (Jiao <i>et al</i> , 2011)	4.49	0% (0/6)	-	0% (0/6)
Germany, 1981-1986 (Schwarze <i>et al</i> , 1989)	-	-	-	21% (3/14)
Germany, 1999-2013 (Barikbin <i>et al</i> , 2016)	-	-	-	14% (2/14)
Hong Kong, 1990-1991 (Leung <i>et al</i> , 1994)	-	50% (2/4)	-	50% (2/4)

Table 1 (continued)

Country, study period (reference)	Incidence (per 10,000 births)	CFR		
		EOL	LOL	Total
India, 2005 (Srivastava <i>et al</i> , 2005)	-	0% (0/1) <sup>***</sup>	-	0% (0/1)
India, 2010 (Mokta <i>et al</i> , 2010)	-	100% (1/1)	-	100% (1/1)
Israel, 1995-1999 (Siegman-Igra <i>et al</i> , 2002)	1.4	16% (3/19) <sup>**</sup>	0% (0/3)	14% (3/22)
Japan, 2000 (Ichiba <i>et al</i> , 2000)	-	0% (0/1)	-	0% (0/1)
Kuwait, 1985-1986 (Dhar, 1988)	-	60% (3/5) <sup>*</sup>	0% (0/4)	33% (3/9)
Netherlands, 1985-1986 (Valkenburg <i>et al</i> , 1988)	-	50% (2/4)	-	50% (2/4)
New Zealand, 1980 (Lennon <i>et al</i> , 1984)	-	-	-	7% (1/14)
Scotland, 1987-1989 (Fyfe <i>et al</i> , 1991)	-	50% (8/16)	0% (0/3)	42% (8/19)
Spain, 1990-1996 (Nolla-Salas <i>et al</i> , 1998)	0-4.1	8% (1/12) <sup>**</sup>	0% (0/1)	8% (1/13)
Taiwan, 1990-2007 (Hsieh <i>et al</i> , 2009)	-	29% (4/14) <sup>*</sup>	-	29% (4/14)
Taiwan, 1990-2011 (Hong and Yang, 2012)	-	33% (2/6)	-	33% (2/6)
Thailand, 1991-2016 (This study)	0.18	14% (1/7) <sup>*</sup>	0% (0/1)	12.5% (1/8)
Thailand, 2013 (Lawtongkum and Thisyakorn, 2016)	-	50% (1/2)	-	50% (1/2)
UK, 1967-1985 (McLauchlin, 1990)	-	38% (40/104) <sup>**</sup>	24% (7/29)	35% (47/133)
UK, 1979 (Robertson <i>et al</i> , 1979)	-	0% (0/1)	-	0% (0/1)
UK, 1988 (Smyth and Bamford, 1988)	-	50% (2/4)	-	50% (2/4)
UK, 2004-2014 (Sapuan <i>et al</i> , 2017)	0.34	22% (4/18) <sup>***</sup>	0% (0/1)	21% (4/19)
USA, 1974-1978 (Halliday and Hirata, 1979)	-	33% (3/9) <sup>***</sup>	0% (0/3)	25% (3/12)
USA, 1982-1989 (Cherubin <i>et al</i> , 1991)	-	-	-	38% (22/58)
USA, 1986 (Gellin <i>et al</i> , 1991)	0.8-2.4	(-/32) <sup>***</sup>	(-/7)	3% (1/39)
USA, 1987 (Teberg <i>et al</i> , 1987)	-	-	-	22% (5/23)
USA, 1992-2013 (Lee <i>et al</i> , 2016)	1.75	-	-	-
Total	-	33% (78/237)	16% (7/45)	28% (151/531)

\* <3 days. \*\* <5 days. \*\*\* <7 days. EOL, early-onset listeriosis; LOL, late-onset listeriosis.

Table 2  
Maternal postnatal conditions, neonatal manifestations and daily hospital cost of listeriosis cases in hospitals, Thailand, 1991-2016.

Hospital <sup>a</sup>	Sex	Date of admittance (month/year)	Onset (hour)	Gestational age (week)	Birth weight (g)	Maternal postnatal condition	Neonatal manifestation	Daily hospital cost (USD) <sup>b</sup>
Songklanagarind	M	4/2014	1	38	2,700	Fever	MAS, severe PPHN	217.22
	F	5/2014	59	40	3,262	Fever	MAS	78.54
	M	3/2016	69	37	2,880	None	Pneumonia, septic shock	193.47
	M	11/2016	15 d	37	2,696	None	Sepsis	160.15
Vachira Phuket	M	11/2013	1	34	2,830	Fever, diarrhea, septic shock, and <i>Listeria</i> bacteremia	Sepsis	-
	M	3/2016	1	36	2,690	Fever	Sepsis	-
Trang	M	1/2016	43	30	1,700	None	Sepsis, RDS, PPHN, death	361.94
Nakhon Pathom	M	3/2016	18	38	3,080	None	Sepsis	38.65

<sup>a</sup>From 11 hospitals surveyed. <sup>b</sup>USD 1 = 30 Baht. F, female; M, male; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome.

The majority of listeriosis cases were male (male:female = 7:1) (Table 2). Three (37%) neonates with listeriosis were preterm, 2 (25%) had MAS but none had meningitis or skin manifestations. The only LOL case was an infant from Myanmar who was born in Songklanagarind Hospital with subgaleal hematoma, jaundice and anemia due to G-6-PD deficiency; against medical advice mother removed the infant from the hospital, but was readmitted in Hat Yai Hospital with neonatal sepsis, seizure and severe jaundice, and eventually was discharged at 30 days of age.

Case-fatality rate (CFR) was 1/8 (12%), being a preterm neonate (gestational age of 30 weeks) with respiratory distress syndrome, PPHN, disseminated intravascular coagulopathy and metabolic acidosis; death occurred on the 4<sup>th</sup> day of life (Table 2). The overall mean (SD) length of hospital stay and daily hospital costs was 16 (7) days and USD 175.0 (114.2) (USD 1 = 30 Baht), respectively.

Antibiograms were based on routinely available antibiotic database at each study hospital. All tested isolates (reported in only three antibiograms) were susceptible to both ampicillin and gentamicin (data not shown).

## DISCUSSION

Our multicenter study confirmed neonatal listeriosis is very rare in Thailand, with an overall incidence of 0.18/10,000 live births over the period 1991-2016. This is notably lower than in most other reports, which range from 0.8-4.5/10,000 live births (Table 1). Globally Southeast Asian countries has the lowest incidence of neonatal group B Streptococcal (GBS) sepsis (0.2/10,000 live births) (Edmond *et al*, 2012), with Thailand having 1.2/10,000

live births (Thatrimontrichai *et al*, 2017), which is 7 times more prevalent than neonatal listeriosis observed in this study. In the USA there is a statistically significant correlation between yearly rates of listeriosis and early-onset GBS (rho factor = 0.53;  $p = 0.01$ ) following the introduction of intrapartum antibiotic prophylaxis ("collateral benefit" effect) (Lee *et al*, 2016).

Among the neonate patients, all listeriosis cases presented during 2013-2016. It is unlikely that during 1991-2012 any occurrence of listeriosis in neonates would have gone undetected as *Listeria* has historically been very rare in Thailand and any indication of the presence of this organism would have resulted in a blood culture test, a routine procedure performed in all hospitals in the country including those in our survey. From a review of the literature, CFR of EOL, LOL and overall neonatal listeriosis is 33%, 16% and 28%, respectively (Table 1), the latter being two times higher than observed in the current survey.

In China the ratio of male:female of neonatal listeriosis is 1.6:1, with peak seasonal distribution of listeriosis (Feng *et al*, 2013) similar to this study and comparable to a study from western Australia, which found peak incidence of listeriosis (10/12 cases) to be during the Australian summer months (January-March), the hottest and driest period of the year (Niels le Souef and Walters, 1981).

This study has a number of limitations. Firstly, it was retrospective, using hospital-based data, so that the number of EOL sepsis cases probably represents the true number, whereas that of LOL sepsis cases may not be accurate because a proportion of neonates may not have returned to the study hospital for treatment. Secondly, the majority of the hospitals in

the study had incomplete medical records and thus a (small) number of cases may have been missed. Thirdly, diseases, outbreaks and health care systems change over time making it difficult to compare data and make sound conclusions. Fourthly, lumbar punctures were not performed in all sepsis cases as many neonates were not amenable to have this procedure. Fifthly, post-mortems were not performed in all cases and thus the number of meningitis cases may be underreported. Sixthly, *Listeria* serotypes were not determined.

In conclusion, our study demonstrates neonatal listeriosis is a rare disease in Thailand and with a lower case-fatality rate than reported in other countries.

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#### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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