

Supplemental Online Content

Brumbaugh JE, Bell EF, Do BT, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Incidence of and neurodevelopmental outcomes after late-onset meningitis among children born extremely preterm. *JAMA Netw Open*. 2022;5(12):e2245826. doi:10.1001/jamanetworkopen.2022.45826

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Newborn Hospitalization Morbidities and Outcomes

Outcomes	n	Infants with LOM n=167	n	Infants with LOS and No LOM n=4564	n	Infants with No LOS or LOM n=8641	P-value ^a
Early-onset sepsis ^b , n (%)	167	3 (2)	4563	84 (2)	8640	219 (3)	0.037
Late-onset blood culture negative clinical infection ^c , n (%)	167	91 (54)	4563	2385 (52)	8634	4136 (48)	<0.001
Severe intracranial hemorrhage ^d , n (%)	166	51 (31)	4520	911 (20)	8536	1517 (18)	<0.001
Periventricular leukomalacia	166	18 (11)	4533	278 (6)	8548	412 (5)	<0.001
Bronchopulmonary dysplasia ^e , n (%)	133	88 (66)	3599	2477 (69)	7172	3917 (55)	<0.001
Necrotizing enterocolitis, n (%)	167	29 (17)	4560	829 (18)	8640	803 (9)	<0.001
Failed hearing screen, n (%)	165	20 (12)	4520	491 (11)	8514	843 (10)	0.166
Retinopathy of prematurity (any stage), n (%)	142	106 (75)	3672	2981 (81)	7114	4951 (70)	<0.001
Intervention for retinopathy of prematurity, n (%)	74	21 (28)	2094	550 (26)	4058	687 (17)	<0.001
Surgery, any, n (%)	167	45 (27)	4564	1390 (30)	8640	1468 (17)	<0.001

^a P-values were calculated from chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables.

^b Early-onset sepsis defined as culture-confirmed bloodstream infection occurring within the first 72 hours and accompanied by ≥5 days of antibiotics.

^c Episode of late-onset infection occurring after 72 hours treated with antibiotics for ≥5 days during the newborn hospitalization.

^d Severe intracranial hemorrhage was defined as Papile grade III or IV.¹⁵

^e Bronchopulmonary dysplasia was defined as respiratory support at 36 weeks' postmenstrual age.

eTable 2. Logistic Regression Model for Risk of Late-Onset Meningitis

Characteristics	Unadjusted results		Adjusted results ^a	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Gestational age (weeks)	0.80 (0.70-0.92)	0.002	0.86 (0.74-1.01)	0.059
Birth year	0.92 (0.89-0.96)	<0.001	0.93 (0.89-0.97)	0.002
Multiple gestation	1.00 (0.70-1.43)	0.997	1.18 (0.81-1.72)	0.387
Private medical insurance	0.69 (0.49-0.97)	0.030	0.76 (0.53-1.08)	0.127
Antenatal steroids	1.18 (0.74-1.88)	0.499	1.51 (0.90-2.53)	0.122
Male	0.89 (0.66-1.21)	0.460	0.87 (0.63-1.20)	0.392
Small for gestational age	0.78 (0.40-1.54)	0.476	0.81 (0.39-1.67)	0.561
Severe ICH ^b (grade III or IV)	1.94 (1.39-2.71)	<0.001	1.81 (1.26-2.61)	0.001

^a Odds ratio and p-values are from logistic regression model which included all covariates listed in table and center.

^b ICH, intracranial hemorrhage.

eTable 3. Distribution of Pathogens Identified in Cerebrospinal Fluid

Pathogen	Infants with late-onset meningitis ^a (n=167)	
	n	%
Bacterial		
Coagulase-negative <i>Staphylococcus</i>	98	58.7
<i>Escherichia coli</i>	27	16.2
<i>Klebsiella spp.</i>	15	9.0
Group B <i>Streptococcus</i>	15	9.0
<i>Enterococcus spp.</i>	15	9.0
<i>Staphylococcus aureus</i>	14	8.4
<i>Streptococcus viridans</i>	4	2.4
<i>Serratia spp.</i>	3	1.8
Other	3	1.8
Fungal		
<i>Candida albicans</i>	38	22.8
<i>Candida parapsilosis</i>	6	3.6
Other	1	0.6

^a Polymicrobial late-onset meningitis was included in analyses if concurrent late-onset sepsis with the same pathogen was identified.

eTable 4. Rate of Lumbar Puncture Performance by Late-Onset Sepsis Pathogen, 2011-2017

LOS Pathogen	LOS Cases ^a n	Lumbar Puncture Performed Ever n (%)	Lumbar Puncture within 7 Days of LOS n (%)
Gram positive bacteria			
Coagulase negative <i>Staphylococcus</i>	716	332 (46)	227 (32)
<i>Staphylococcus aureus</i>	261	135 (52)	107 (41)
<i>Enterococcus</i>	61	34 (56)	24 (39)
Group B <i>Streptococcus</i>	60	50 (83)	43 (72)
Other Gram positive bacteria	28	12 (43)	4 (14)
Gram negative bacteria			
<i>Escherichia coli</i>	137	68 (50)	55 (40)
<i>Klebsiella</i>	90	56 (62)	43 (48)
<i>Pseudomonas</i>	62	26 (42)	18 (29)
<i>Enterobacter</i>	37	29 (78)	23 (62)
Other Gram negative bacteria	40	26 (65)	18 (45)
Fungus			
<i>Candida</i>	61	40 (66)	23 (38)
Other fungus	2	1 (50)	1 (50)
Other pathogen			
Other bacteria Gram stain unknown	12	7 (58)	6 (50)
Other	17	9 (53)	7 (41)

^a Excludes polymicrobial LOS.

eTable 5. Logistic Regression Models for Risk of Neurodevelopmental Impairment or Death

Characteristics	Unadjusted results		Adjusted results ^a	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Model for risk of NDI^b or death (composite)				
Gestational age (weeks)	0.61 (0.59-0.63)	<0.001	0.62 (0.60-0.65)	<0.001
Birth year	0.99 (0.98-1.00)	0.103	1.00 (0.99-1.01)	0.580
Multiple gestation	1.05 (0.97-1.15)	0.232	1.14 (1.03-1.26)	0.010
Private medical insurance	0.62 (0.58-0.67)	<0.001	0.64 (0.58-0.70)	<0.001
Antenatal steroids	0.59 (0.53-0.66)	<0.001	0.81 (0.71-0.92)	0.002
Male	1.45 (1.35-1.56)	<0.001	1.45 (1.33-1.58)	<0.001
Small for gestational age	2.75 (2.34-3.22)	<0.001	3.84 (3.22-4.58)	<0.001
Severe ICH ^c (grade III or IV)	3.57 (3.22-3.96)	<0.001	3.15 (2.80-3.54)	<0.001
Infection status				
LOM ^d	1.81 (1.29-2.53)	0.001	1.53 (1.04-2.25)	0.032
LOS ^e and no LOM ^d	1.66 (1.53-1.79)	<0.001	1.41 (1.29-1.54)	<0.001
No LOS ^e or LOM ^d	REF		REF	
Model for risk of NDI^b				
Gestational age (weeks)	0.72 (0.69-0.75)	<0.001	0.72 (0.68-0.76)	<0.001
Birth year	1.03 (1.01-1.04)	<0.001	1.02 (1.00-1.03)	0.017
Multiple gestation	1.03 (0.93-1.14)	0.525	1.14 (1.02-1.28)	0.025
Private medical insurance	0.62 (0.56-0.68)	<0.001	0.64 (0.57-0.71)	<0.001
Antenatal steroids	0.69 (0.61-0.79)	<0.001	0.86 (0.74-1.00)	0.052
Male	1.45 (1.33-1.59)	<0.001	1.46 (1.33-1.62)	<0.001
Small for gestational age	2.05 (1.70-2.48)	<0.001	2.56 (2.08-3.15)	<0.001
Severe ICH ^c (grade III or IV)	2.23 (1.97-2.52)	<0.001	2.09 (1.82-2.40)	<0.001
Infection status				
LOM ^d	1.49 (0.98-2.24)	0.059	1.26 (0.79-2.01)	0.337
LOS ^e and no LOM ^d	1.54 (1.40-1.69)	<0.001	1.34 (1.20-1.49)	<0.001
No LOS ^e or LOM ^d	REF		REF	
Model for risk of death				
Gestational age (weeks)	0.57 (0.55-0.59)	<0.001	0.58 (0.55-0.61)	<0.001
Birth year	0.95 (0.94-0.96)	<0.001	0.96 (0.95-0.97)	<0.001
Multiple gestation	1.06 (0.96-1.17)	0.225	1.10 (0.98-1.23)	0.096
Private medical insurance	0.74 (0.68-0.81)	<0.001	0.77 (0.69-0.85)	<0.001

Characteristics	Unadjusted results		Adjusted results ^a	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Antenatal steroids	0.58 (0.52-0.65)	<0.001	0.83 (0.72-0.95)	0.008
Male	1.27 (1.16-1.38)	<0.001	1.23 (1.12-1.36)	<0.001
Small for gestational age	2.58 (2.24-2.97)	<0.001	4.04 (3.42-4.78)	<0.001
Severe ICH ^c (grade III or IV)	3.92 (3.55-4.32)	<0.001	3.39 (3.03-3.79)	<0.001
Infection status				
LOM ^d	1.85 (1.32-2.61)	0.001	1.33 (0.89-1.97)	0.161
LOS ^e and no LOM ^d	1.52 (1.40-1.66)	<0.001	1.23 (1.11-1.36)	<0.001
No LOS ^e or LOM ^d	REF		REF	

^a Odds ratio and p-values are from logistic regression model which included all covariates listed in the table and center.

^b NDI, neurodevelopmental impairment.

^c ICH, intracranial hemorrhage.

^d LOM, late-onset meningitis.

^e LOS, late-onset sepsis.

eTable 6. Outcomes at 18 to 26 Months' Corrected Age by Late-Onset Meningitis Pathogen Classification

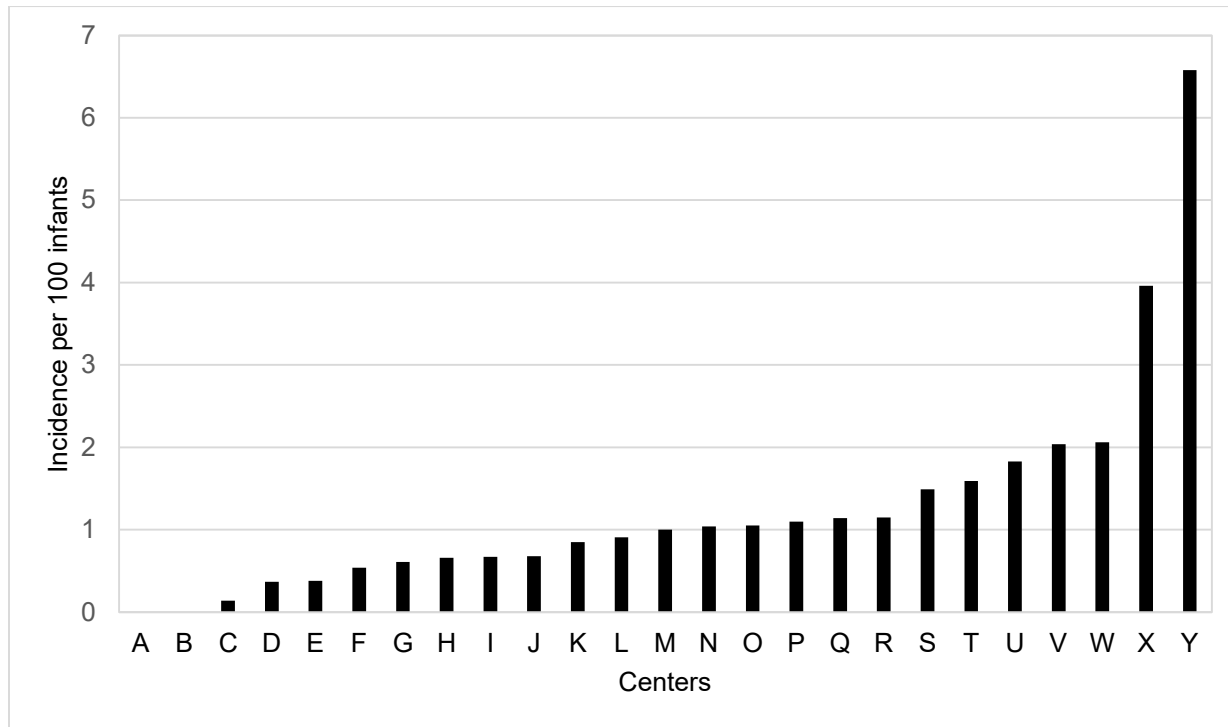
Characteristics	n	CoNS^a LOM n=47	n	Non-CoNS^a Bacterial LOM n=70	n	Fungal LOM n=34	P-value^b
NDI ^c or Death	46	22 (48)	67	43 (64)	33	26 (79)	0.018
NDI ^c	36	12 (33)	39	15 (38)	20	13 (65)	0.059
Death	47	10 (21)	70	28 (40)	34	13 (38)	0.091

^a CoNS, coagulase negative *Staphylococcus*.

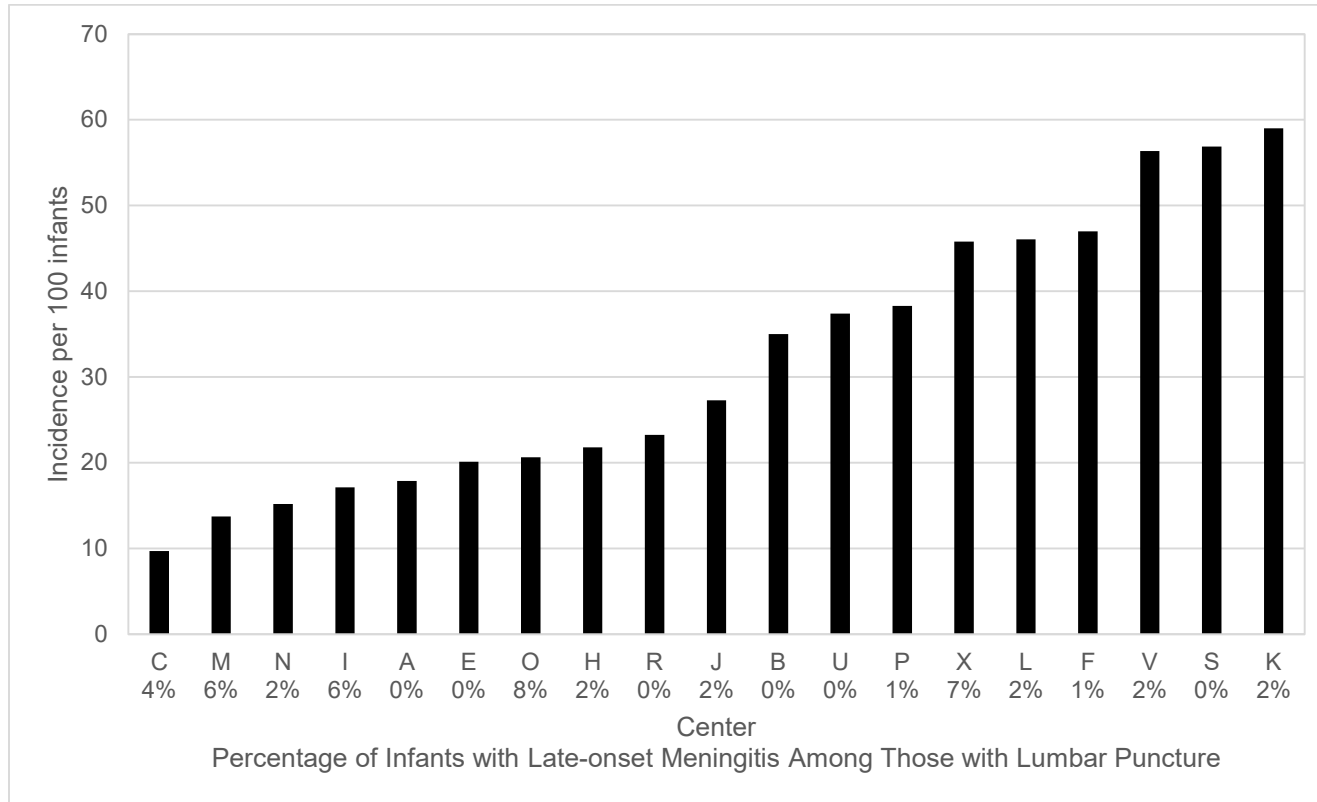
^b P-values were calculated from chi-square tests.

^c NDI, neurodevelopmental impairment.

eFigure 1. Incidence of Detected Late-Onset Meningitis by Center (2003-2017)

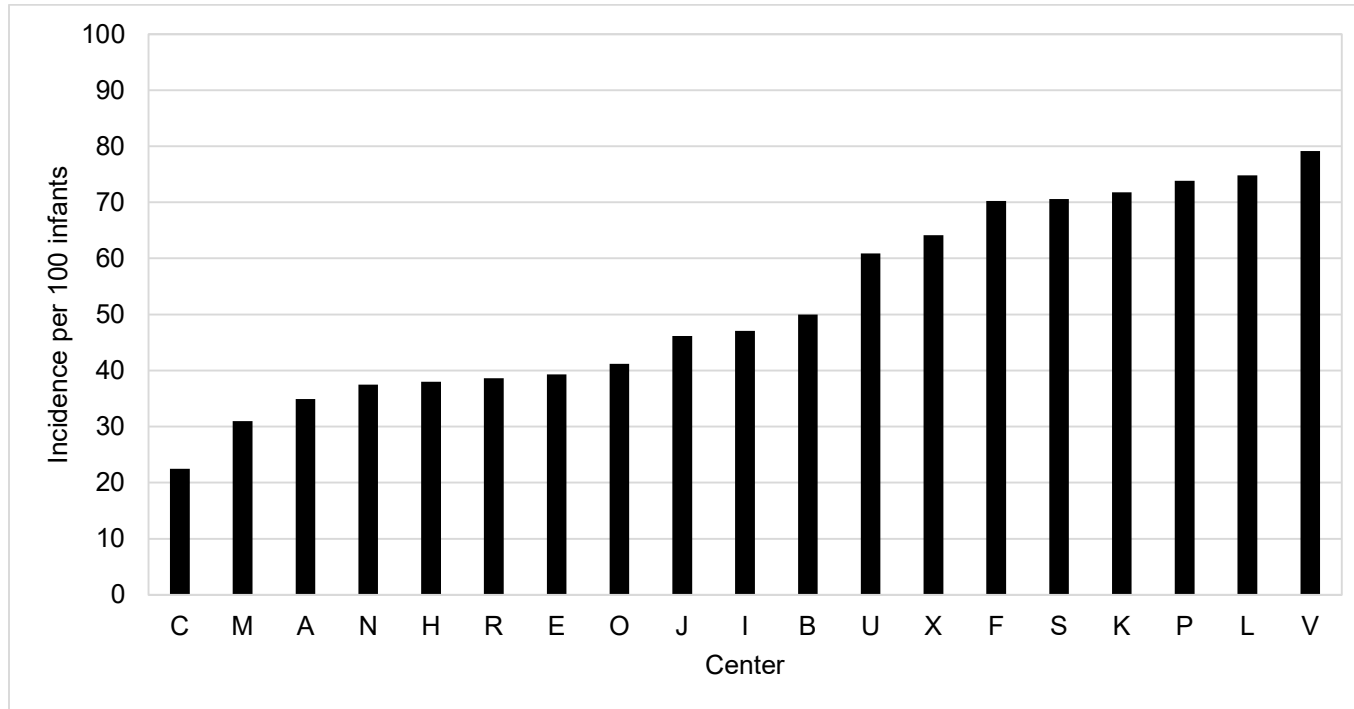


eFigure 2. Incidence of Lumbar Puncture (LP) in Late-Onset Sepsis Evaluations by Center, and Percentage of Infants Diagnosed with Late-Onset Meningitis (2011-2017)^a



^aThere were six fewer centers in the NRN for the period 2011-2017 compared to the full period 2003-2017. The centers are represented by the same letter in eFigures 1-3.

eFigure 3. Incidence of Lumbar Puncture Among Infants with Culture-confirmed Late-Onset Sepsis by Center (2011-2017)^a



^aThere were six fewer centers in the NRN for the period 2011-2017 compared to the full period 2003-2017. The centers are represented by the same letter in eFigures 1-3.