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A Decade of Sepsis Cases in a Level III Neonatal Intensive Care Unit: An Observational Study

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Abstract:

Background: *Neonatal sepsis is a serious condition caused largely by group B Streptococcus (GBS), Escherichia coli (E. Coli), and Listeria monocytogenes. Prenatal screenings have decreased the incidence of GBS infections; however, it remains a leading cause of early-onset sepsis (EOS). Gram-positive organisms are often the cause of late-onset sepsis (LOS). While EOS is usually attributed to vertical transmission from mother to infant, LOS is secondary to pathogen exposure during delivery or hospitalization. We sought to identify the prevalent organisms in positive blood cultures in our NICU.*

Methods: *A retrospective chart review was completed from July 2009 to December 2019. If an organism was identified, a positive culture was included, and five or more days of antibiotics were administered. Infection occurring in the first three days of life was considered EOS, while LOS was any time after. Variables were evaluated using Fisher's exact and Wilcoxon rank-sum tests.*

Results: *Over ten years, there were 89 positive blood cultures. Of these, 28% of the cases were EOS, and 72% were LOS. Interestingly, the median birth weight for infants with EOS was significantly larger at 1810g compared to 1021g for LOS (P=0.004). The median gestational age for EOS cases was 31 5/7 weeks compared to 27 2/7 weeks for LOS (P=0.086).*

Conclusions: *Approximately half of EOS-causing organisms were GBS or E.Coli. Coagulase-negative staphylococcus and methicillin-susceptible Staphylococcus aureus were most prevalent in LOS.*

Abbreviations

CoNS	Coagulase-Negative Staphylococcus
DOL	Day of Life
EOS	Early Onset Sepsis
E. Coli	*Escherichia coli*
GA	Gestational Age
GBS	Group B *Streptococcus*
LOS	Late-Onset Sepsis
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*

Main points:

A ten-year review of sepsis in infants in NICU with positive cultures confirmed that over half of early-onset sepsis cases contained GBS and *E.Coli.* CoNS and MSSA were most prevalent in late-onset sepsis.

Keywords:

Neonatal Sepsis; Blood Culture; Intensive Care Units, Neonatal; Infant, Newborn;

"Approximately half of EOS-causing organisms were GBS or E.Coli. Coagulase-negative staphylococcus and methicillin-susceptible Staphylococcus aureus were most prevalent in LOS."

Introduction:

Neonatal sepsis is a serious threat affecting the health and survival of infants worldwide. It occurs in 1-50 per 1000 live births and causes 3-30% of infant and child deaths yearly. (1) In the United States of America, the incidence of neonatal sepsis is 0.77-1.0 cases per 1000 live births but rises to a rate of 8-26 cases per 1000 live births for infants between 1000-1500 grams (g). (2) Research has consistently shown a strong inverse relationship between gestational age (GA) and the incidence of sepsis. (3-7)

" Neonatal sepsis cases are categorized as early-onset sepsis (EOS) occurring within the first 72 hours of life or late-onset sepsis (LOS) developing after 72 hours with pathogens transmitted from the mother's genitourinary system before, during, or shortly after birth as the usual the cause. (1-3,8-9)"

Neonatal sepsis cases are categorized as early-onset sepsis (EOS) occurring within the first 72 hours of life or late-onset sepsis (LOS) developing after 72 hours with pathogens transmitted from the mother's genitourinary system before, during, or shortly after birth as the usual the cause. (1-3,8-9) Risk factors include antenatal antibiotics, maternal chorioamnionitis, multiple pregnancies, maternal Group B *Streptococcus* (GBS) colonization, maternal urinary tract infection, delivery before 37 weeks GA, prolonged maternal rupture of membranes (greater than 18 hours), low 5-minute APGAR score, and those requiring ventilation on the first day of life (DOL). (2,4,8) *Escherichia coli* (E. coli) and GBS are consistently the leading causes of EOS in the United States, with a prevalence of 29-37% and 18-43%, respectively. (2,4,8-11)This trend holds for most developed countries worldwide. (12-18) Among infants infected with GBS, about one-quarter progress in developing meningitis requiring prolonged antibiotic treatment and hospitalization with increasing chances of morbidity. (19-20) Other less common EOS organisms include *Listeria monocytogenes*; other strains of streptococcus (*pyogenes, viridans, pneumoniae*); enterococci, staphylococci, and non-typeable *Haemophilus influenzae*. (2,4,8)

Late-onset sepsis (LOS) occurs after 72 hours of life and is usually caused by pathogens in the surrounding environment, often transmitted to the infant by parents or health care workers. (1,2,8) The risk factors include premature birth, being small for GA, antenatal antibiotic use, delivery via Cesarean section, prolonged use of invasive interventions, breakage in skin or mucosa, prolonged total parenteral nutrition dependence, delayed initiation of breastmilk feeding, surgery, cardiac/pulmonary abnormalities, necrotizing enterocolitis, H_2-receptor blockage or proton pump inhibitor, and/or prolonged antibiotic use. (1,3,8,21) Coagulase-negative staphylococcus (CoNS) is the most common LOS pathogen in the United States of America, with other developed countries presenting similar results. (4,6,12-13,22-29)

"Interestingly, each NICU has its microbiome, and specific pathogens are common as the cause of sepsis at each site. (5) The objective of our study was to identify the most prevalent types of organisms in blood cultures for both EOS and LOS in our NICU over ten years."

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Methods:

Data were collected retrospectively from Valleywise Health Medical Center (formally known as Maricopa Medical Center), a 40-bed level III community NICU in Phoenix, Arizona, from July 2009 through December 2019. Researchers collected data on positive blood cultures using the Epic Electronic Health Record system (Epic Systems Corporation, Verona, WI). In the event of CoNS bacteremia, or another suspected contaminant, at least one positive blood culture and a full antibiotic treatment course with a clinical picture consistent with sepsis needed to be included. If there was a positive blood culture and it was not treated with antibiotics due to the absence of clinical sepsis, this was considered a contaminant and excluded. Infections were categorized as EOS if the septic workup occurred within the first three days of life, while LOS was defined as a sepsis workup initiated at DOL four or greater.

Statistical analysis included the association between categorical variables of EOS and LOS utilizing Fisher's exact tests. The differences in continuous variables were examined using the Wilcoxon rank-sum test. Human protection oversight was provided by the Maricopa Health Institutional Review Board, later known as Valleywise Health Institutional Review Board.

Results:

Over ten years, 89 blood cultures were positive. The infants with positive septic workups were 54% female (n=48), had a median GA of 28 1/7 weeks (22 5/7- 41 6/7), and median birth weight of 1155g (486-4240g). The median initiation of antibiotic treatment was at DOL 0 (0-292) with a median duration of 12 days (0-47) (Tables 1 & 2).

		EOS	LOS		
		n (%)		N	*P**
Gender	Female	16 (64)	32 (50)	48	0.249
	Male	9 (36)	32 (50)	41	
Mode of delivery	Cesarean	14 (56)	38 (59.38)	52	0.814
	Vaginal	11 (44)	26 (40.63)	37	
Mortality	No	20 (80)	50 (78.13)	70	>0.999
	Yes	5 (20)	14 (21.88)	19	
	Total	25	64	89	
*Fisher's exact 2-sided *P* value					

Table 1. Gender, Mode of Delivery, and Mortality

The most common pathogens were CoNS (23.6% of total positive cultures, n=21), methicillin-susceptible *staphylococcus aureus* (MSSA) (20.3%, n= 13), *E coli* (13.5%, n=12), GBS (10.1%, n=9), *enterococcus faecalis* (9.0%, n=8), and *klebsiella pneumoniae* (7.9%, n=7). No other organism was isolated more than four times (Table 3).

Of the 89 total positive blood cultures, 28% were considered EOS (n=25) while 72% were LOS (n=64). Gender, GA, mode of delivery, and mortality were not significantly different between EOS and LOS infants (Table 1). On average, EOS infants were somewhat smaller, with a median birth weight of 1810 g, while LOS infants had a median birth weight of 1021g (*P*=0.004). Infants with EOS also received a slightly shorter course of antibiotics, with a median duration of 11.0 days, compared to a median duration of 12.5 days for LOS infants (*P*=0.045). As expected, antibiotic treatment was initiated at a significantly younger age for EOS and the median initial treatment day was 0 with a mean of 0.14, while the median and mean initial treatment day of LOS infants was 6, with a mean of 22.4 (*P*<0.0001).

	All Culture Positive Sepsis						Type of Sepsis											
							Early (<3 days) Onset (n=25)						Late (4+ days) Onset (n=64)					
	N*	Mean	Median	Min	Max	SD	n*	Mean	Median	Min	Max	SD	n*	Mean	Median	Min	Max	SD	P**
Gestational Age, Weeks/Days	89	29 6/7	28 1/7	22 5/7	41 6/7	37.96	25	31 6/7	31 5/7	23 3/7	41 2/7	43.28	64	29 1/7	27 2/7	22 5/7	41 6/7	34.52	0.086
Birthweight, Grams	89	1553.43	1155	486	4240	968.21	25	2098.8	1810	486	4240	1175.78	64	1340.39	1021	530	3758	786.53	**0.004**
Duration of Treatment, Days	77	14.22	12	0	47	9.89	21	9.81	11	0	22	6.17	56	15.88	12.5	2	47	10.54	**0.045**
Initiation of Treatment, Day of Life	87	16.54	0	0	292	47.31	23	0.13	0	0	2	0.46	64	22.44	6	0	292	54.05	**<.0001**

*Some counts may be less than total due to missing values
**Wilcoxon rank-sum test comparing variables in the first column between EOS and LOS groups

Table 2. Gestational Age, Birthweight, Duration, and Initiation of Treatment

	n (% of cultures)		
	EOS	LOS	Total
Coagulase-negative staphylococcus	2 (8)	19 (26.4)	23 (23.7)
Methicillin-susceptible *Staphylococcus aureus*	0 (0)	13 (18.1)	13 (13.4)
Escherichia coli	6 (24)	6 (8.3)	12 (12.4)
Group B *Streptococcus*	7 (28)	2 (2.8)	9 (9.3)
Enterococcus faecalis	2 (8)	6 (8.3)	8 (8.2)
Klebsiella pneumoniae	1 (4)	6 (8.3)	7 (7.2)
Candida albicans	0 (0)	4 (5.6)	4 (4.1)
Listeria moncytogenes	1 (4)	2 (2.8)	3 (3.1)
Coagulase-positive staphylococcus	0 (0)	3 (4.2)	3 (3.1)
Micrococcus luteus	2 (8)	0 (0)	2 (2.1)
Corynebacterium species	1 (4)	0 (0)	1 (1.0)
Haemophilus influenza	1 (4)	0 (0)	1 (1.0)
Streptococcus pseudopneumoniae	1 (4)	0 (0)	1 (1.0)
Streptococcus viridans	1 (4)	0 (0)	1 (1.0)
Brevundimonas vesicularis	0 (0)	1 (1.4)	1 (1.0)
Enterobacter cloacae	0 (0)	1 (1.4)	1 (1.0)
Gram-positive cocci in clusters	0 (0)	1 (1.4)	1 (1.0)
Klebsiella oxytoca	0 (0)	1 (1.4)	1 (1.0)
Methicillin-resistant *Staphylococcus aureus*	0 (0)	1 (1.4)	1 (1.0)
Proteus mirabilis	0 (0)	1 (1.4)	1 (1.0)
Pseudomonas aeruginosa	0 (0)	1 (1.4)	1 (1.0)
Serratia marcescens	0 (0)	1 (1.4)	1 (1.0)
Streptococcus acidominimus	0 (0)	1 (1.4)	1 (1.0)
Streptococcus bovis	0 (0)	1 (1.4)	1 (1.0)
Streptococcus pneumoniae	0 (0)	1 (1.4)	1 (1.0)
Total	**25**	**72**	**97**

LOS Blood Culture Pairs	**n**
Methicillin-susceptible *Staphylococcus aureus*/ Coagulase-negative staphylococcus	2
Methicillin-susceptible *Staphylococcus aureus*/ Coagulase-positive *Staphylococcus aureus*	2
Coagulase-negative staphylococcus/*Brevundimonas veiscularis*	1
Enterococcus faecalis/*Escherichia coli*	1
Enterococcus faecalis/*Klebsiella pneumoniae*	1
Staphylococcus epidermidis/*Staphylococcus hominis* (Coagulase-negative staphylococcus x2)	1
Total	**8**

Table 3. Pathogens Present in Blood Cultures

There were 25 cases of EOS that were culture positive with a single pathogen, and there were no blood cultures positive for multiple species of bacteria. The most common being GBS (28%, n=7) and *E. coli* (24%, n=6). (Table 3) Late-onset sepsis accounted for 64 total cases of positive culture results, with 72 pathogens isolated, with the most prevalent as follows: CoNS (26.4%, n=19), MSSA (18.1%, n=13), *E. coli* (8.3%, n=6), *Enterococcus faecalis* (8.3%, n=6), and *Klebsiella pneumonia* (8.3%, n=6). There were three cultures containing coagulase-positive staphylococcus; however, the exact speciation was not recorded in the medical record. Eight blood cultures were positive for two different microorganisms with CoNS. No other pathogen was isolated more than two times. Only one blood culture was confirmed to have methicillin-resistant *Staphylococcus aureus* (MRSA), and another was positive for nonspecific gram-positive cocci in clusters.

Two separate pathogens were present in eight of the LOS blood cultures. (Table 3) Of these, two blood cultures were positive for both MSSA and an unspecified coagulase-positive *staphylococcus aureus*, and it is unclear whether it represented MSSA or MRSA. During some septic workups, cultures were obtained from other sites. Interestingly, only two infants with EOS had a positive blood culture and a positive culture from another site of a different pathogen, one of which had *E. coli* in the blood and a urine culture positive for cytomegalovirus, and the other, with *Haemophilus influenzae* in the blood and cerebrospinal fluid positive for herpes simplex virus. All remaining positive cultures from sites other than blood were in cases of LOS (n=21) (Table 4).

"Data collected over a ten-year duration showed that GBS was the most commonly occurring EOS organism, followed by E. coli. Of note, none of the infants' mothers received prophylactic antibiotics in all four cases of GBS sepsis."

Discussion:

Data collected over a ten-year duration showed that GBS was the most commonly occurring EOS organism, followed by *E. coli*. Of note, none of the infants' mothers received prophylactic antibiotics in all four cases of GBS sepsis. Since the initiation of GBS screening in the 1990s, the incidence has decreased by 70-80% in the United States of America, with a similar decline in other

Urine	
Candida albicans	2
Enterococcus faecalis	2
Candida albicans/Coagulase-negative staphylococcus	1
Enterococcus faecium	1
Cerebral Spinal Fluid	
Candida albicans	1
Escherichia coli	1
Enterococcus faecalis	1
Generically positive	1
Endotracheal	
Escherichia coli	2
Acinetobacter baumannii/*Enterobacter cloacae*	1
Methicillin-susceptible *Staphylococcus aureus*	1
Methicillin-susceptible *Staphylococcus aureus*/*Stenotrophomonas maltophilia*	1
Klebsiella pneumoniae/*Pseudomonas aeruginosa*/*Serratia marcescens*	1
Peritoneal	
Group B *Streptococcus*	1
Methicillin-resistant *Staphylococcus aureus*	1
Klebsiella aerogenes/*Klebsiella oxytoca*	1
Klebsiella pneumoniae	1
Wound	
Escherichia coli	1
Total	**21**

Table 4. Pathogens Present in Non-Blood Cultures

developed countries. (1,8) Despite this, it continues to be a leading cause of EOS in the United States of America and most other industrialized countries, and our findings are consistent with this previous research. Stoll et al. collected data from 16 large NICUs across the country from 2006 to 2009 and found that GBS was the most common offending pathogen in 43% of cases, followed by *E. coli* in 29% of cases. (10) Simonsen et al. reported at the North American Active Bacterial Surveillance Program from 2005 to 2008 that 33.7% of positive cultures isolated GBS, while 21.5% isolated *E. coli.* (2) Other studies have shown *E. coli* as the most prevalent NICU pathogen for EOS. Drs. Mukhopadhyay and Puopolo retrospectively reviewed 25 years of blood cultures at Boston's Brigham Women and Children's NICU from 1990 to 2015 and found 36.7% of positive EOS blood cultures, with GBS being only 20.2% of positive cultures. (11) Bizarro et al. (22) from the Yale University NICU reviewed data from 2004 to 2013 and found *E. coli* to account for 45% of EOS and GBS to be only 36%. Hornik et al. (4) reviewed data from 313 NICUs across North America and estimated *E. coli* to be the most common EOS pathogen at 33.4%, followed by GBS at 21.5% (although this was limited to infants <1500g). In all of these studies, GBS was the second-most common EOS pathogen, similar to our study's results. Besides *E. coli*, only two cases of other Gram-negative EOS were identified over ten years in our NICU: *Klebsiella pneumoniae* and *Haemophilus influenzae*.

Although *Listeria monocytogenes* was historically a common cause of neonatal sepsis, its prevalence remains relatively low at 2-13 per 100,000 live births in the United States of America and Europe. (2) Our NICU isolated only a single case of *Listeria monocytogenes* over ten years, consistent with previous studies. One meta-analysis from six hospital systems across the United States over six years did not find a single case of neonatal *Listeria* bacteremia in181 positive blood cultures. (30)

"For ten years, CoNS was the most common pathogen of LOS, followed by staphylococcus aureus. This agrees with many other studies conducted throughout the United States of America. (4,6,21,22)"

For ten years, CoNS was the most common pathogen of LOS, followed by *staphylococcus aureus*. This agrees with many other studies conducted throughout the United States of America. (4,6,21,22) Coagulase-negative staphylococcus is also the most-commonly isolated LOS pathogen throughout the developed and developing world. (22-29,31-35)The CoNS organism is not as virulent as many other types of bacteria, but it commonly colonizes human skin, mucous membranes, and artificial surfaces, forming an adhesive biofilm resistant to antibiotics and the immune system. (3,8) There is some difficulty in comparisons as most studies have unique definitions of contamination versus infection. Studies have also reported that efforts to implement improved hand hygiene and sterile technique with central lines can decrease late-onset CoNS infection rates.

Gram-negative LOS was more common in our NICU than gram-negative EOS (outside of *E. coli* bacteremia). However, they remained in the minority of bacteremia cases, and many specific Gram-negative species were isolated only once. Although our study did have a sizable number of cases of Gram-negative sepsis, even those not caused by *E. coli*, our LOS sepsis results were consistent with most studies.

Conclusions:

In our study, the most common cause of EOS was *E. coli,* followed by GBS and α-hemolytic streptococcus. This is in agreement with most NICU sepsis research. The most common cause of LOS was CoNS, which is consistent with most studies across the world, among all regions, races, and incomes.

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This study's strengths include a ten-year data collection period at a single medical center that serves a diverse population in one of the largest metropolitan areas in the United States of America. As this study was retrospective, its strength was in capturing the standard care practices occurring in the unit; however, this also may be seen as a limitation as to the decision of when to initiate

a sepsis workup could have varied between providers in addition to the antimicrobials used in the event of positive blood culture.

Limitations of this study are the relatively small sample size, its execution at a single medical center that may not be representative of other NICUs, and that we did not focus on the effect that race and/or ethnicity may have played at our institution. A large-scale prospective study would be helpful to evaluate these findings further and assist with the generalizability to other NICUs.

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References:

1. *Ershad M, Mostafa A, Dela Cruz M, Vearrier D. Neonatal Sepsis. Curr Emerg Hosp Med Rep. 2019;7(3):83-90. doi: 10.1007/s40138-019-00188-z. Epub 2019 Jun 19. PMID: 32226657; PMCID: PMC7100521.*
2. *Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014 Jan;27(1):21-47. doi: 10.1128/CMR.00031-13. PMID: 24396135; PMCID: PMC3910904.*
3. *Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed. 2015 May;100(3):F257-63. doi: 10.1136/archdischild-2014-306213. Epub 2014 Nov 25. PMID: 25425653; PMCID: PMC4413803.*
4. *Hornik CP, Fort P, Clark RH, Watt K, Benjamin DK Jr, Smith PB, Manzoni P, Jacqz-Aigrain E, Kaguelidou F, Cohen-Wolkowiez M. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Hum Dev. 2012 May;88 Suppl 2(Suppl 2):S69-74. doi: 10.1016/S0378-3782(12)70019-1. PMID: 22633519; PMCID: PMC3513766.*
5. *Tsai MH, Hsu JF, Chu SM, Lien R, Huang HR, Chiang MC, Fu RH, Lee CW, Huang YC. Incidence, clinical characteristics and risk factors for adverse outcome in neonates with late-onset sepsis. Pediatr Infect Dis J. 2014 Jan;33(1):e7-e13. doi: 10.1097/INF.0b013e3182a72ee0. PMID: 23899966.*
6. *Boghossian NS, Page GP, Bell EF, Stoll BJ, Murray JC, Cotten CM, Shankaran S, Walsh MC, Laptook AR, Newman NS, Hale EC, McDonald SA, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. J Pediatr. 2013 Jun;162(6):1120-4, 1124.e1. doi: 10.1016/j.jpeds.2012.11.089. Epub 2013 Jan 13. PMID: 23324523; PMCID: PMC3633723.*
7. *Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, Robinson MJ, Collinson A, Heath PT. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed. 2011 Jan;96(1):F9-F14. doi: 10.1136/adc.2009.178798. Epub 2010 Sep 27. PMID: 20876594.*
8. *Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am. 2013 Apr;60(2):367-89. doi: 10.1016/j.pcl.2012.12.003. Epub 2013 Jan 17. PMID: 23481106; PMCID: PMC4405627.*
9. *Glaser MA, Hughes LM, Jnah A, Newberry D. Neonatal Sepsis: A Review of Pathophysiology and Current Management Strategies. Adv Neonatal Care. 2021 Feb 1;21(1):49-60. doi: 10.1097/ANC.0000000000000769. PMID: 32956076.*
10. *Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, Bizzarro MJ, Goldberg RN, Frantz ID 3rd, Hale EC, Shankaran S, Kennedy K, Carlo WA, Watterberg KL, Bell EF, Walsh MC, Schibler K, Laptook AR, Shane AL, Schrag SJ, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics. 2011 May;127(5):817-26. doi: 10.1542/peds.2010-2217. Epub 2011 Apr 25. Erratum in: Pediatrics. 2011 Aug;128(2):390. PMID: 21518717; PMCID: PMC3081183.*
11. *Mukhopadhyay S, Puopolo KM. Clinical and Microbiologic Characteristics of Early-onset Sepsis Among Very Low Birth Weight Infants: Opportunities for Antibiotic Stewardship. Pediatr Infect Dis J. 2017 May;36(5):477-481. doi: 10.1097/INF.0000000000001473. PMID: 28403049; PMCID: PMC6009981.*
12. *Fernandez Colomer B, Cernada Badia M, Coto Cotallo D, Lopez Sastre J; Grupo Castrillo Network. The Spanish National Network "Grupo Castrillo": 22 Years of Nationwide Neonatal Infection Surveillance. Am J Perinatol. 2020 Sep;37(S 02):S71-S75. doi: 10.1055/s-0040-1714256. Epub 2020 Sep 8. PMID: 32898887.*
13. *Giannoni E, Agyeman PKA, Stocker M, Posfay-Barbe KM, Heininger U, Spycher BD, Bernhard-Stirnemann S, Niederer-Loher A, Kahlert CR, Donas A, Leone A, Hasters P, Relly C, Riedel T, Kuehni C, Aebi C, Berger C, Schlapbach LJ; Swiss Pediatric Sepsis Study. Neonatal Sepsis of Early Onset, and Hospital-Acquired and Community-Acquired Late Onset: A Prospective Population-Based Cohort Study. J Pediatr. 2018 Oct;201:106-114.e4. doi: 10.1016/j.jpeds.2018.05.048. Epub 2018 Jul 24. PMID: 30054165.*
14. *Kim SJ, Kim GE, Park JH, Lee SL, Kim CS. Clinical features and prognostic factors of early-onset sepsis: a 7.5-year experience in one neonatal intensive care unit. Korean J Pediatr. 2019 Jan;62(1):36-41. doi: 10.3345/kjp.2018.06807. Epub 2018 Sep 27. PMID: 30304900; PMCID: PMC6351802.*
15. *Cailes B, Kortsalioudaki C, Buttery J, Pattnayak S, Greenough A, Matthes J, Bedford Russell A, Kennea N, Heath PT; neonIN network. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. Arch Dis Child Fetal Neonatal Ed. 2018 Nov;103(6):F547-F553. doi: 10.1136/archdischild-2017-313203. Epub 2017 Dec 5. PMID: 29208666.*
16. *Mintz A, Mor M, Klinger G, Scheuerman O, Pirogovsky A, Sokolover N, Bromiker R. Changing epidemiology and resistance patterns of pathogens causing neonatal bacteremia. Eur J Clin Microbiol Infect Dis. 2020 Oct;39(10):1879-1884. doi: 10.1007/s10096-020-03921-9. Epub 2020 May 15. PMID: 32415489.*
17. *Liu J, Fang Z, Yu Y, Ding Y, Liu Z, Zhang C, He H, Geng H, Chen W, Zhao G, Liu Q, Wang B, Sun X, Wang S, Sun R, Fu D, Liu X, Huang L, Li J, Xing X, Wang X, Gao Y, Zhu R, Han M, Peng F, Geng M, Deng L. Pathogens distribution and antimicrobial resistance in bloodstream infections in twenty-five neonatal intensive care units in China, 2017-2019. Antimicrob Resist Infect Control. 2021 Aug 16;10(1):121. doi: 10.1186/s13756-021-00989-6. PMID: 34399840; PMCID: PMC8365905.*
18. *Khalil N, Blunt HB, Li Z, Hartman T. Neonatal early onset*

sepsis in Middle Eastern countries: a systematic review. Arch Dis Child. 2020 Jul;105(7):639-647. doi: 10.1136/archdischild-2019-317110. Epub 2020 Jan 22. PMID: 31969351.

19. *de Gier B, van Kassel MN, Sanders EAM, van de Beek D, Hahné SJM, van der Ende A, Bijlsma MW. Disease burden of neonatal invasive Group B Streptococcus infection in the Netherlands. PLoS One. 2019 May 9;14(5):e0216749. doi: 10.1371/journal.pone.0216749. PMID: 31071191; PMCID: PMC6508726.*
20. *Madrid L, Seale AC, Kohli-Lynch M, Edmond KM, Lawn JE, Heath PT, Madhi SA, Baker CJ, Bartlett L, Cutland C, Gravett MG, Ip M, Le Doare K, Rubens CE, Saha SK, Sobanjo-Ter Meulen A, Vekemans J, Schrag S; Infant GBS Disease Investigator Group. Infant Group B Streptococcal Disease Incidence and Serotypes Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017 Nov 6;65(suppl_2):S160-S172. doi: 10.1093/cid/cix656. PMID: 29117326; PMCID: PMC5850457.*
21. *Testoni D, Hayashi M, Cohen-Wolkowiez M, Benjamin DK Jr, Lopes RD, Clark RH, Benjamin DK, Smith PB. Late-onset bloodstream infections in hospitalized term infants. Pediatr Infect Dis J. 2014 Sep;33(9):920-3. doi: 10.1097/INF.0000000000000322. PMID: 24618934; PMCID: PMC4160433.*
22. *Bizzarro MJ, Shabanova V, Baltimore RS, Dembry LM, Ehrenkranz RA, Gallagher PG. Neonatal sepsis 2004-2013: the rise and fall of coagulase-negative staphylococci. J Pediatr. 2015 May;166(5):1193-9. doi: 10.1016/j.jpeds.2015.02.009. PMID: 25919728; PMCID: PMC4413005.*
23. *Cantey JB, Pyle AK, Wozniak PS, Hynan LS, Sánchez PJ. Early Antibiotic Exposure and Adverse Outcomes in Preterm, Very Low Birth Weight Infants. J Pediatr. 2018 Dec;203:62-67. doi: 10.1016/j.jpeds.2018.07.036. Epub 2018 Aug 29. PMID: 30172430.*
24. *El Manouni El Hassani S, Berkhout DJC, Niemarkt HJ, Mann S, de Boode WP, Cossey V, Hulzebos CV, van Kaam AH, Kramer BW, van Lingen RA, van Goudoever JB, Vijlbrief DC, van Weissenbruch MM, Benninga MA, de Boer NKH, de Meij TGJ. Risk Factors for Late-Onset Sepsis in Preterm Infants: A Multicenter Case-Control Study. Neonatology. 2019;116(1):42-51. doi: 10.1159/000497781. Epub 2019 Apr 4. PMID: 30947195; PMCID: PMC6690411.*
25. *Wu IH, Tsai MH, Lai MY, Hsu LF, Chiang MC, Lien R, Fu RH, Huang HR, Chu SM, Hsu JF. Incidence, clinical features, and implications on outcomes of neonatal late-onset sepsis with concurrent infectious focus. BMC Infect Dis. 2017 Jul 3;17(1):465. doi: 10.1186/s12879-017-2574-7. PMID: 28673280; PMCID: PMC5496375.*
26. *Mariani M, Parodi A, Minghetti D, Ramenghi LA, Palmero C, Ugolotti E, Medici C, Saffioti C, Castagnola E. Early and Late Onset Neonatal Sepsis: Epidemiology and Effectiveness of Empirical Antibacterial Therapy in a III Level Neonatal Intensive Care Unit. Antibiotics (Basel). 2022 Feb 21;11(2):284. doi: 10.3390/antibiotics11020284. PMID: 35203886; PMCID: PMC8868064.*
27. *Berlak N, Shany E, Ben-Shimol S, Chertok IA, Goldinger G, Greenberg D, Melamed R. Late onset sepsis: comparison between coagulase-negative staphylococci and other bacteria in the neonatal intensive care unit. Infect Dis (Lond). 2018 Oct;50(10):764-770. doi: 10.1080/23744235.2018.1487075. Epub 2018 Jul 3. PMID: 29969049.*
28. *Wójkowska-Mach J, Gulczyńska E, Nowiczewski M, Borszewska-Kornacka M, Domańska J, Merritt TA, Helwich E, Kordek A, Pawlik D, Gadzinowski J, Szczapa J, Adamski P, Sulik M, Klamka J, Brzychczy-Włoch M, Heczko PB. Late-onset bloodstream infections of Very-Low-Birth-Weight infants: data from the Polish Neonatology Surveillance Network in 2009-2011. BMC Infect Dis. 2014 Jun 18;14:339. doi: 10.1186/1471-2334-14-339. PMID: 24939563; PMCID: PMC4074408.*
29. *Li X, Ding X, Shi P, Zhu Y, Huang Y, Li Q, Lu J, Li Z, Zhu L. Clinical features and antimicrobial susceptibility profiles of culture-proven neonatal sepsis in a tertiary children's hospital, 2013 to 2017. Medicine (Baltimore). 2019 Mar;98(12):e14686. doi: 10.1097/MD.0000000000014686. PMID: 30896617; PMCID: PMC6709008.*
30. *Biondi E, Evans R, Mischler M, Bendel-Stenzel M, Horstmann S, Lee V, Aldag J, Gigliotti F. Epidemiology of bacteremia in febrile infants in the United States. Pediatrics. 2013 Dec;132(6):990-6. doi: 10.1542/peds.2013-1759. Epub 2013 Nov 11. Erratum in: Pediatrics. 2014 Apr;133(4):754. PMID: 24218461.*
31. *Gul A, Takci S. Analysis of late-onset neonatal sepsis cases in a level three neonatal intensive care unit. North Clin Istanb. 2020 May 28;7(4):354-358. doi: 10.14744/nci.2019.39018. PMID: 33043260; PMCID: PMC7521094.*
32. *Hammoud MS, Al-Taiar A, Al-Abdi SY, Bozaid H, Khan A, AlMuhairi LM, Rehman MU. Late-onset neonatal sepsis in Arab states in the Gulf region: two-year prospective study. Int J Infect Dis. 2017 Feb;55:125-130. doi: 10.1016/j.ijid.2017.01.006. Epub 2017 Jan 11. PMID: 28088587.*
33. *Pillay D, Naidoo L, Swe Swe-Han K, Mahabeer Y. Neonatal sepsis in a tertiary unit in South Africa. BMC Infect Dis. 2021 Feb 27;21(1):225. doi: 10.1186/s12879-021-05869-3. PMID: 33639864; PMCID: PMC7912533.*
34. *Quispe AM, Soza G, Ramos Chirinos M, Quiroz D, Pons MJ. Multidrug resistance bacteremia in neonates and its association with late-onset sepsis and Coagulase-negative Staphylococci. J Infect Dev Ctries. 2020 Nov 30;14(11):1256-1263. doi: 10.3855/jidc.12568. PMID: 33296338.*
35. *Shehab El-Din EM, El-Sokkary MM, Bassiouny MR, Hassan R. Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt. Biomed Res Int. 2015;2015:509484. doi: 10.1155/2015/509484. Epub 2015 Jun 4. PMID: 26146621; PMCID: PMC4471255.*

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