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Evaluation of Molecular Diagnostic Results in Iraqi Newborns with Sepsis

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Abstract: Background and Aim: Sepsis is a major cause of disease and death in newborns. This study largely aims to assess the outcomes of newborns with sepsis who underwent to molecular diagnostics.

Methods: A study was conducted in hospitals in Baghdad, Iraq, on 66 infants during the follow-up period from March 2023 to March 2024. Patient data were extracted and analyzed using SPSS 22.0 on Iraqi newborn patients with sepsis. Our study recorded patient and clinical data, including demographics, maternal and neonatal characteristics, symptoms, and etiologies, which were analyzed for their impact on neonatal outcomes in the hospital.

Results: Based on our outcomes, all 66 patients' data were collected from hospitals. In terms of early-onset sepsis (EOS), we found fever got 88.89% and low birth weight (92.59%) were considered as the most common symptom and cause prevalence in patients, GBS (33.33%), E. COIL (25.93%), hospital stays (28.5 ± 3.4) days, mortality (22.22%), serious brain injury (22.22%), and retinopathy of prematurity ≥ 2 (33.33%). In terms of late-onset sepsis (LOS), it observed patients' data following feeding intolerance got 75.0%, respiratory distress (35.0%), and coagulase-negative staphylococci (CoNS) (57.50%), staphylococcus aureus (67.50%) were considered as the most common symptom

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and cause prevalence in patients, CONS (55.0%), E. COIL (12.5%), hospital stays (11.6 ± 2.6) days, mortality (5.0%), serious brain injury (5.0%), and retinopathy of prematurity ≥ 2 (7.5%).

Conclusion: Sepsis continues to be associated with a higher risk of mortality and longer stays in hospitals, along with more chances of brain damage in survivors, although we have noted a decline in those patients with late-onset sepsis in juxtaposition to patients suffering from early-onset sepsis.

Key words: Sepsis; Newborns; Molecular diagnostic.

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by an unregulated host response to infection [1]. Neonatal sepsis affects babies up to 28 days old and is a major cause of morbidity and mortality of newborns [2]. The incidence of neonatal sepsis varies between different geographical areas, although it has been estimated that in the world population, 2202 neonatal sepsis per 100,000 live births develop neonatal sepsis, with a mortality of 11-19% [3,4]. In the USA, sepsis of bacterial origin that occurs in newborns is the second leading cause of death, and an incidence of 4.7 to 32.8 events per 1000 newborns is reported. [5]

Early-onset sepsis (EOS) is defined as the onset of sepsis in the first 3 days of birth and is mainly the result of the vertical transmission of bacteria: mothers to babies during the intrapartum period. LOS is defined as the infection that occurs after 1 week of life and is attributed to the horizontal transmission of pathogens acquired after birth. [6,7,8,9]

The signs and symptoms of neonatal sepsis include fever or hypothermia, respiratory difficulty including cyanosis and apnea, difficulty eating, lethargy or irritability, hypotonia, convulsions, bulging fontanelle, poor perfusion, bleeding problems, abdominal distension, hepatomegaly since the clinical picture is very general, neonatal sepsis could be indistinguishable from other diseases, which makes its diagnosis based solely on the symptomatology very difficult. [10,11]

The assessment of molecular diagnoses in neonates with sepsis portrays the inadequacies of traditional methods as well as the promise of more advanced novel techniques [12]. Current diagnostic practices that assess the blood cultures from specimens require long periods before their results are available, usually yielding low sensitivity; these factors have clearly negative impacts on treatment outcomes. Potential new-age forms of molecular methodologies: multiplex PCR and next-generation sequencing (NGS), promise to improve diagnostic precision and speed and further enhance clinical decision-making. [13.14.15]

On the other hand, the amount of the inoculum is important for this test; approximately 6 ml of blood is required to optimize the results, and its sensitivity is decreased by the low volume of blood used; for this reason, it is one of the great disadvantages of using the “gold standard” in the diagnosis of neonatal sepsis, because it is not feasible to obtain that volume of blood from a newborn. [16]

Patients and methods

I. Study Design

This cross-sectional study was conducted in different hospitals in Iraq, focusing on newborns with sepsis during the period between March 2023 and March 2024. Sixty-six newborns with a final diagnosis of sepsis were included in the study. The major aim was to assess the outcome of newborns with sepsis using molecular diagnostic methods (PCR) culture.

II. Collected Data

Such renowned demographic and clinical characteristics comprise age, gender, birth weight, gestational age, and mode of delivery (e.g., cesarean section). Maternal characteristics collected in

this study include age, parity, and any maternal infection or complication in pregnancy. All patients diagnosed in the hospitals showed symptoms at presentation (fever, respiratory distress, feeding intolerance), etiologies, and clinical outcomes (mortality, hospital stay duration, complications such as necrotizing enterocolitis, retinopathy of prematurity, and serious brain injury). Molecular diagnostic results (PCR) and blood culture results were kept for the identification of causative agents.

III. Inclusion and Exclusion Criteria

- Inclusion Criteria

Neonates showing signs of sepsis (fever, respiratory distress, feeding intolerance) up to 28 days old. Molecular diagnostic (PCR) and blood culture results were available.

- Exclusion Criteria

Newborns with congenital defects or other severe illness not related to sepsis. Incomplete clinical or laboratory data. Molecular Diagnostic (PCR) and Blood Culture. Multiplex PCR was used to find pathogens in blood samples. This method is much better than traditional blood cultures because of its high sensitivity and specificity. Blood samples were cultured to identify bacterial pathogens. The volume of blood used for culture was optimized to increase sensitivity, though this remains a challenge in neonates. Example pathogens include - Group B Streptococcus (GBS), Escherichia coli (E. coli), coagulase-negative staphylococci (CoNS), and Staphylococcus aureus.

IV. Statistical Analysis

The statistical analysis was carried out with the aid of SPSS 22.0 for conducting the descriptive statistics, which were supposed to summarize the demographic and clinical characteristics. - For categorical variables (symptoms, etiologies, mortality rates), frequencies and percentages were calculated. Whereas mean and standard deviation were used for continuous variables (hospital stay duration). A comparative analysis was done between early other onset sepsis (EOS) and late-onset sepsis (LOS) for outcome differences. - investigated the association between pathogen burden and clinical outcomes (e.g., mortality, complications) using regression models.

Results

Our study describes the demographic and clinical characteristics of the study population. These demographics and clinical characteristics were summed up and discussed in terms of the newborns that were included in the study. The greatest ages were in between ages 31 – 35 years, with 34 cases.

Table 1: Demographic features observed in this study.

GROUPS	VARIABLES	NO OF PATIENTS, (66)	PERCENTAGE, %
AGE, YEARS			
	25 – 30	18	27.27%
	31 – 35	34	51.52%
	36 – 40	14	21.21%
BODY MASS INDEX (KG/M2)			
	Underweight	4	6.06%
	Normal weight	11	16.67%
	Overweight	21	31.82%
	Obesity	30	45.45%
COMORBIDITY			
	No	22	33.33%
	Hypertension	28	42.42%
	Amnionitis	5	7.58%
	Preeclampsia	8	12.12%
	Gestational diabetes	13	19.70%

	Others	6	9.09%
SMOKING STATUS			
	Present	8	12.12%
	Absent	58	87.88%
ANTENATAL ANTIBIOTICS			
	Present	23	34.85%
	Absent	43	65.15%
WORKING STATUS			
	Housewife	40	60.61%
	Employed	26	39.39%
EDUCATION STATUS			
	Primary	11	16.67%
	Secondary	18	27.27%
	Post graduated university	37	56.06%
ECONOMIC STATUS, $			
	< 500	26	39.39%
	500 – 700	22	33.33%
	> 700	18	27.27%

The data reveal that the great majority of cases were preterm under the low-birth-weight category in less than 1.5 37.88% under multiple births (22.73%) under caesarian section (60.61%), which all newborns suffer from a high risk of death, which coincides with the already known factors of neonatal sepsis. The predominance of males within this cohort attends previous studies that suggest a higher propensity for developing sepsis in male neonates at 53.03%.

Table 2: Maternal characteristics.

Groups	Variables	No of patients, (66)	Percentage, %
Gestational age, weeks			
	< 27	4	6.06%
	28 – 32	13	19.70%
	33 – 36	29	43.94%
	≥ 36	20	30.30%
Inborn			
	Yes	55	83.33%
	No	11	16.67%
No. of births			
	Single birth	51	77.27%
	Multiple births	15	22.73%
Antenatal steroids			
	None, less than 24 h	24	36.36%
	One dose within 24 h	42	63.64%
Types of mode			
	Vaginal	26	39.39%
	Caesarean section	40	60.61%

Table 3: Characteristics of neonatal.

Categories	Parameters	No. of patients, 66	Percentage, %
Birth weight			
	< 1.5	25	37.88%
	1.5 – 2.2	32	48.48%
	> 2.2	9	13.64%

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Sex			
	Male	35	53.03%
	Female	31	46.97%
Newborn			
	Singular	62	93.94%
	Twin	4	6.06%
APGAR Score			
	Apgar <7 at 1 min	44	66.67%
	Apgar <7 at 5 min	22	33.33%
Mode of feeding			
	Breastmilk	38	57.58%
	Formula	21	31.82%
	Mixed	7	10.61%
Ventilation		48	72.73%
Continuous positive airway pressure			
	Yes	45	68.18%
	No	21	31.82%
Major anomaly			
	Yes	6	9.09%
	No	62	93.94%
Antibiotics given			
	Yes	66	100%
	No	0	0%
Antibiotic days per sepsis episode		9.38 ± 1.21	

Targeted monitoring and early intervention in high-risk populations are underscored by findings. Results also reflected the frequencies of the pathogens detected by molecular diagnostic methods. Thus, the causal agents in terms of the most frequently detected pathogens from this region include Escherichia coli (25.93%), cons (55.0%), GBS (33.33%), and Staphylococcus aureus (10.0%). Empirical antibiotic regimens suitable for those pathogens present in Iraqi neonatal units should be highlighted due to the high detection rate of gram-negative bacteria.

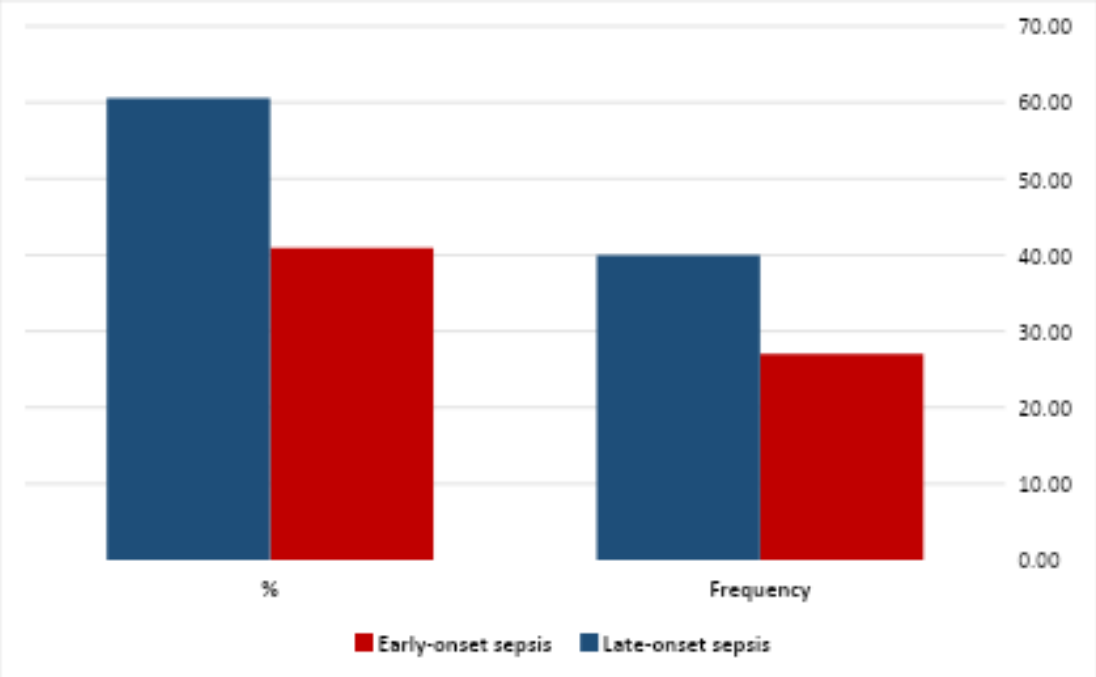

Figure 1: Identify newborns' sepsis in terms of early-onset sepsis and late-onset sepsis.

Table 4: Enroll clinical characteristics of symptoms and causes in terms of early-onset sepsis and late-onset sepsis detected by molecular diagnostic.

Categories	Parameters	Frequency	Percentage, %
EOS		27	40.91%
Symptoms			
	Fever	24	88.89%
	Lethargy	20	74.07%
	Poor feeding	16	59.26%
	Respiratory distress	4	14.81%
	Hypotonia	2	7.41%
	Vomiting	9	33.33%
	Diarrhea	6	22.22%
	Low blood pressure	12	44.44%
	Tachycardia	5	18.52%
Causes			
	Early-Onset Sepsis (EOS)	23	85.19%
	Maternal infections	17	62.96%
	Low birth weight	25	92.59%
	Prematurity	11	40.74%
	Premature rupture of membranes (PROM)	2	7.41%
	Chorioamnionitis	9	33.33%
	Maternal fever during labor	7	25.93%
LOS		40	60.61%
Symptoms			
	Feeding intolerance	30	75.0%
	Abdominal distension	5	12.5%
	Temperature instability	21	52.5%
	Respiratory distress	14	35.0%
	Seizures	1	2.5%
	Jaundice	2	5.0%
	Grunting	1	2.50%
	Irritability	8	20.0%
Causes			
	Hospital-acquired infections	6	15.0%
	Exposure to bacteria from caregivers	3	7.50%
	Coagulase-negative staphylococci (CoNS)	23	57.50%
	Staphylococcus aureus	27	67.50%
	Pseudomonas	14	35.0%

Table 5: Distribution of blood isolates of neonatal for each early – onset sepsis and late-onset sepsis.

ITEMS	BLOOD ISOLATES	FREQUENCY	PERCENTAGE, %
EARLY–ONSET SEPSIS		**27**	**40.91%**
	GBS	9	33.33%
	E. COIL	7	25.93%
	H. INFLUENZAE	3	11.11%
	S. PNEUMONIA	3	11.11%
	CONS	2	7.41%
	S. AUREUS	1	3.70%
	E. FAECALIS	2	7.41%

	S. VIRIDANS	9	33.33%
LATE-ONSET SEPSIS		**40**	**60.61%**
	CONS	22	55.0%
	E. COIL	5	12.5%
	S. AUREUS	4	10.0%
	KLEBSIELLA PNEUMONIA	3	7.50%
	GBS	3	7.50%
	ENTEROCOCCUS FAECALIS	1	2.50%
	S. MARCESCENS	1	2.50%

E. coli and K. pneumoniae were found to be more prominent in the first week of life, while S. aureus was more commonly isolated in the second week. The order that emerges points to a temporal existence of early-onset sepsis, which is presumed to be mainly of gram-negative etiology, while late-onset sepsis tends to be of gram-positive origin.

Table 6: Enroll post outcomes at hospital discharge for neonatal patients.

PARAMETERS	EARLY-ONSET SEPSIS, {N = 27}		LATE-ONSET SEPSIS, {N = 40}	
HOSPITAL STAYS, DAYS, MEAN ± SD	28.5 ± 3.4		11.6 ± **2.6**	
DEATH CASE, N {%}				
YES	6	22.22%	2	5.0%
NO	21	77.78%	38	95.0%
NECROTISING ENTEROCOLITIS IN EQUAL OR ABOVE GRADE 3, N {%}				
YES	2	7.41%	0	0%
NO	25	92.59%	40	100%
RETINOPATHY OF PREMATURITY ≥ 2, N {%}				
YES	9	33.33%	3	7.5%
NO	18	66.67%	37	92.5%
SERIOUS BRAIN INJURY, N {%}				
YES	6	22.22%	2	5.0%
NO	21	77.78%	38	95.0%

Furthermore, hospital discharge of patients were enrolled of newborn outcomes after birth status. In EOS outcomes, we noticed that hospital stays was 28.5 ± 3.4 days, mortality rate with 22.22%, Necrotising enterocolitis in equal or above grade 3 got 2 cases, retinopathy of prematurity ≥2 had 9 cases, and serious brain injury with 6 cases. In LOS outcomes, we noticed that hospital stays was 11.6 ± 2.6 days, mortality rate with 5%, necrotising enterocolitis in equal or above grade 3 got 0 cases, retinopathy of prematurity ≥2 had 3 cases, and serious brain injury with 2 cases.

The molecular approach, providing significantly higher sensitivity and specificity, was capable of detecting pathogens even when cultures yielded negative results. This emphasizes the drawbacks of traditional methods while building a case for molecular diagnostics to serve as reliable tools for the early diagnosis of sepsis. The strong association indicates that increasing the pathogen burden may lead to worsening clinical manifestations. This points to the potential of using quantitative molecular assays for predicting disease severity and guiding treatment decisions. We have Antimicrobial Resistance Patterns of Identified Pathogens that are outlined in this paper and describe the antimicrobial resistance patterns of the pathogens identified through this study. The fact that most of these organisms are multi-drug resistant, especially gram-negative, raises questions about the efficacies of conventional antibiotics.

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Discussion

It is conceivable to run basic tests, albeit tests for pathogen range might as well be recommended till an infection is detected. Broad-range PCR can be implemented on this blood specimen. [17]

In this study, with slightly more than 66 neonates, a 5.0% decline in LOS was seen. While gram-positive organisms were the most common blood culture isolate, S. agalactiae was mostly seen in EOS, while CONS was the most in LOS; gram-negative organisms were associated with more mortality in EOS.

Neonatal infants that have early onset sepsis were found to be associated with longer hospital stays and reported to have higher mortality and increasing cases of necrotizing enterocolitis, which have been graded at or above 2, and increased incidence of chronic lung disease. Also, it was found that early- and late-onset sepsis may cause severe brain injuries in Premi babies and mortality, while LOS is linked to an increased length of stay, as well as high mortality and possible cases of NEC >I. [17]

The observed incidence of EOS-0.6/1,000 live births is comparable to that of other areas in Australia and other high-income countries. Nevertheless, there was a decrease in the number of S. agalactiae isolates from infants aged 27-35 weeks of gestation [18]. Intrapartum antibiotic prophylaxis introduced in the early 1990s was associated with a number of declines in EOS as per various studies from Australasia between 1992 and 2006, which predated the present study and correlated with the sharpest decline in EOS [19,20].

The LOS rates of 14.7%, 3.2%, and 0.1% in neonates <28 weeks, 28–31+6, and ≥32 weeks of gestation, respectively, are in line with or below those from other high-income countries like the USA and Canada [21]. The observed decrease in LOS, which is majorly on account of decreased CONS, can be attributed to certain changes in routine management of the most vulnerable infants implemented in our setting, such as probiotic supplementation, early introduction, and rapid advancement of enteral feeds; the use of topical coconut oil to protect skin integrity; improvement in insertion techniques and increased monitoring of intravenous cannulas; and general awareness about hand hygiene. [22]

The pattern of early-onset sepsis pathogens closely resembled those of other countries; S. agalactiae and E. coli were most frequently identified [23]. Similar to the findings of other centers, GBS and E. COIL were the most important organisms in EOS in infants, with 33.33% and 25.93%, respectively, of the total patients and mostly in those <31 weeks of gestation and S. agalactiae mostly positive in infants >31 weeks. Some has reported a vast marginal decrease in the early-onset sepsis (EOS) incidence due to S. agalactiae, which was associated with static or increasing EOS due to E. coli for all gestational age groups.

Like other high-income countries, LOS pathogens in this series included CONS, E. coli, and S. aureus. While more frequent in isolation, gram-positive organisms were associated with fatal outcomes, and gram-negative was at the more than likely age of death [24]. The most recent NeoOBS study also highlights this saying that one of the studies mentioned reported a mortality of 21.3% from gram-negative sepsis as against an 8.5% mortality due to gram-positive sepsis. Over 75% of culture-verified deaths due to sepsis were attributed to gram-negative organisms within that cohort. [25]

The prevalence of meningitis complicating EOS and LOS found in this study was consistent with previous Australian and New Zealand findings [26,27,28]. All positive CSF cultures in this study corresponded to positive blood cultures, but there have been reports of a discrepancy of up to 16-39% between blood and CSF culture results [29]. The approach of performing an LP for suspected meningitis only in cases of positive blood culture would miss a significant number of infants with meningitis. [30]

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Conclusion

Based on our study, molecular diagnostics have significantly contributed to the early detection of pathogens causing sepsis in newborns and the start of adequate antimicrobial therapy that correlates extremely well with outcome. However, neonatal sepsis is a life-threatening condition that causes morbidity and mortality. Our diagnosis has been reduced in the mortality of patients with late-onset sepsis compared with early-onset sepsis.

References

1. Pieren, D.K.J.; Boer, M.C.; de Wit, J. The adaptive immune system in early life: The shift makes it count. Front. Immunol. 2022, 13, 1031924.
2. Glaser, M.A.; Hughes, L.M.; Jnah, A.; Newberry, D. Neonatal Sepsis: A Review of Pathophysiology and Current Management Strategies. Adv. Neonatal Care 2021, 21, 49–60.
3. Shane, A.L.; Sánchez, P.J.; Stoll, B.J. Neonatal sepsis. Lancet 2017, 390, 1770–1780.
4. Cantey, J.B.; Lee, J.H. Biomarkers for the Diagnosis of Neonatal Sepsis. Clin. Perinatol. 2021, 48, 215–227.
5. van Veen, L.E.J.; van der Weijden, B.M.; Achten, N.B.; van der Lee, L.; Hol, J.; van Rossem, M.C.; Rijpert, M.; Oorthuys, A.O.J.; van Beek, R.H.T.; Dubbink-Verheij, G.H.; et al. Incidence of Antibiotic Exposure for Suspected and Proven Neonatal Early-Onset Sepsis between 2019 and 2021: A Retrospective, Multicentre Study. Antibiotics 2024, 13, 537.
6. Schulman, J.; Benitz, W.E.; Profit, J.; Lee, H.C.; Dueñas, G.; Bennett, M.V.; Jocson, M.A.L.; Schutzengel, R.; Gould, J.B. Newborn Antibiotic Exposures and Association With Proven Bloodstream Infection. Pediatrics 2019, 144, e20191105.
7. Kliegman, R.M.; Behrman, R.E.; Jenson, H.B.; Stanton, B.M. Nelson Textbook of Pediatrics E-Book; Elsevier Health Sciences: Amsterdam, The Netherlands, 2007.
8. Osrin, D.; Vergnano, S.; Costello, A. Serious bacterial infections in newborn infants in developing countries. Curr. Opin. Infect. Dis. 2004, 17, 217–224.
9. Oza, S.; Lawn, J.E.; Hogan, D.R.; Mathers, C.; Cousens, S.N. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000–2013. Bull. World Health Organ. 2015, 93, 19–28.
10. Weston, E.J.; Pondo, T.; Lewis, M.M.; Martell-Cleary, P.; Morin, C.; Jewell, B.; Daily, P.; Apostol, M.; Petit, S.; Farley, M.; et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. Pediatr. Infect. Dis. J. 2011, 30, 937–941.
11. Speier, R.L.; Cotten, C.M.; Benjamin, D.K., Jr.; Lewis, K.; Keeler, K.; Kidimbu, G.; Roberts, W.; Clark, R.H.; Zimmerman, K.O.; Stark, A.; et al. Late-Onset Sepsis Evaluation and Empiric Therapy in Extremely Low Gestational Age Newborns. J. Pediatr. Infect. Dis. Soc. 2023, 12, S37–S43.
12. Hayes, R.; Hartnett, J.; Semova, G.; Murray, C.; Murphy, K.; Carroll, L.; Plapp, H.; Hession, L.; O'Toole, J.; McCollum, D.; et al. Neonatal sepsis definitions from randomised clinical trials. Pediatr. Res. 2023, 93, 1141–1148.
13. Perlman, S.E.; Saiman, L.; Larson, E.L. Risk factors for late-onset healthcare-associated bloodstream infections in patients in neonatal intensive care units. Am. J. Infect. Control 2007, 35, 177–182.
14. Lemme-Dumit, J.M.; Song, Y.; Lwin, H.W.; Hernandez-Chavez, C.; Sundararajan, S.; Viscardi, R.M.; Ravel, J.; Pasetti, M.F.; Ma, B. Altered Gut Microbiome and Fecal Immune Phenotype in Early Preterm Infants With Leaky Gut. Front. Immunol. 2022, 13, 815046.

15. Simonsen, K.A.; Anderson-Berry, A.L.; Delair, S.F.; Davies, H.D. Early-Onset Neonatal Sepsis. Clin. Microbiol. Rev. 2014, 27, 21–47.
16. Berlak, N.; Shany, E.; Ben-Shimol, S.; Chertok, I.A.; 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. 2018, 50, 764–770.
17. Cai, S.; Thompson, D.K.; Anderson, P.J.; Yang, J.Y. Short- and Long-Term Neurodevelopmental Outcomes of Very Preterm Infants with Neonatal Sepsis: A Systematic Review and Meta-Analysis. Children 2019, 6, 131.
18. Sewell, E.; Roberts, J.; Mukhopadhyay, S. Association of Infection in Neonates and Long-Term Neurodevelopmental Outcome. Clin. Perinatol. 2021, 48, 251–261.
19. Kaya, G.; Usta, D.; Sag, E.; Aydin, Z.G.; Buruk, C.K.; Ozkaya, E.; Aydin, F.; Cakir, M. Incidence and Risk Factors for Antibiotic-associated Diarrhea Among Hospitalized Children. Pediatr. Infect. Dis. J. 2023, 42, 745–749.
20. Martinez, F.E.; Ferri, W.A.G.; Leone, C.R.; de Almeida, M.F.B.; Guinsburg, R.; Meneses, J.D.A.; Vale, M.S.D.; Marba, S.T.M.; de Carvalho, W.B.; de Souza Rugolo, L.M.S.; et al. Early Empiric Antibiotic Use Is Associated With Delayed Feeding Tolerance in Preterm Infants: A Retrospective Analysis. J. Pediatr. Gastroenterol. Nutr. 2017, 65, 107–110.
21. Abdel Ghany, E.A.; Ali, A.A. Empirical antibiotic treatment and the risk of necrotizing enterocolitis and death in very low birth weight neonates. Ann. Saudi Med. 2012, 32, 521–526.
22. Alexander, V.N.; Northrup, V.; Bizzarro, M.J. Antibiotic exposure in the newborn intensive care unit and the risk of necrotizing enterocolitis. J. Pediatr. 2011, 159, 392–397.
23. Cotten, C.M.; Taylor, S.; Stoll, B.; Goldberg, R.N.; Hansen, N.I.; Sánchez, P.J.; Ambalavanan, N.; Benjamin, D.K., Jr. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 2009, 123, 58–66.
24. Kuppala, V.S.; Meinzen-Derr, J.; Morrow, A.L.; Schibler, K.R. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J. Pediatr. 2011, 159, 720–725.
25. Alonso-Ojembarrena, A.; Martínez-Díaz, J.V.; Lechuga-Sancho, A.M.; Galán-Sánchez, F.; Lubián-López, S.P. Broad spectrum antibiotics in newborns increase multi-drug resistant infections. J. Chemother. 2019, 31, 81–85.
26. Droste, J.H.; Wieringa, M.H.; Weyler, J.J.; Nelen, V.J.; Vermeire, P.A.; Van Bever, H.P. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? Clin. Exp. Allergy 2000, 30, 1547–1553.
27. Duong, Q.A.; Pittet, L.F.; Curtis, N.; Zimmermann, P. Antibiotic exposure and adverse long-term health outcomes in children: A systematic review and meta-analysis. J. Infect. 2022, 85, 213–300.
28. Hoskin-Parr, L.; Teyhan, A.; Blocker, A.; Henderson, A.J. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: A dose-dependent relationship. Pediatr. Allergy Immunol. 2013, 24, 762–771.
29. Lin, Y.C.; Chen, Y.C.; Kuo, C.H.; Chang, Y.H.; Huang, H.Y.; Yeh, W.J.; Wu, T.Y.; Huang, M.Y.; Hung, C.H. Antibiotic exposure and asthma development in children with allergic rhinitis. J. Microbiol. Immunol. Infect. 2020, 53, 803–811.
30. Marra, F.; Marra, C.A.; Richardson, K.; Lynd, L.D.; Kozyrskyj, A.; Patrick, D.M.; Bowie, W.R.; FitzGerald, J.M. Antibiotic Use in Children Is Associated With Increased Risk of Asthma. Pediatrics 2009, 123, 1003–1010.