Mechanism of necrotizing enterocolitis in preterm infants through the hypoxia signaling pathway, neuronal-glial signaling pathway, and intestinal fatty acid signaling pathway

by Dina Angelika

Submission date: 23-May-2023 08:24PM (UTC+0800)
Submission ID: 2100020585
File name: gnaling_pathway,_and_intestinal_fatty_acid_signaling_pathway.pdf (561.46K)
Word count: 3730
Character count: 19159

Mechanism of necrotizing enterocolitis in preterm infants through the hypoxia signaling pathway, neuronal-glial signaling pathway, and intestinal fatty acid signaling pathway

Dina Angelika
Doctoral Program of Medical Science, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia,
(E-mail: dina.angelika-2019@fk.unair.ac.id)

Risa Etika
Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia,
(E-mail: neonatologi.rssoetomo@gmail.com)

I Dewa Gede Ugrasena
Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia,
(E-mail: dewa.gede.ugrasena@fk.unair.ac.id)

ABSTRACT

The etiology of necrotizing enterocolitis (NEC) is influenced by many factors including hypoxia, intestinal immaturity, bacterial colonization, reactive oxidants, and imbalanced inflammatory response; therefore, the pathogenesis of NEC is considered multifactorial. However, the pathogenesis of NEC has not been fully elucidated and requires further investigation. This study aimed to analyze the association between hypoxia inducible factor-1alpha (HIF-1alpha), glial fibrillary acidic protein (GFAP), glial derived neutrophic factor (GDNF), fatty acid binding protein-2 (FABP-2), peroxime proliferator activated receptor-gamma (PPAR-gamma), interleukin-6 (IL-6), and interleukin-8 (IL-8) with the incidence of NEC in preterm infants. All preterm infants with birth weight <1500 grams or gestational age <34 weeks were included in this study. After the umbilical cord was removed, 1 mL of umbilical blood was taken for HIF-1alpha, GFAP, GDNF, FABP-2, PPAR-gamma, IL-6, and IL-8 examination. Examination of HIF-1alpha, GFAP, GDNF, FABP-2, PPAR-gamma, IL-6, and IL-8 was repeated in infants with NEC symptoms using peripheral venous blood specimen. Infants were observed for 2 weeks. NEC was diagnosed based on clinical symptoms and abnormal abdominal radiographs. Of the 30 infants, there were 9 (30%) infants who experienced NEC. Logistic regression analysis showed significant results on GFAP with Odds Ratio (OR)=15.629 (95% confidence interval=1.697-143.906) P=0.015 and FABP-2 with OR=1.008 (1.001-1.015) P=0.033. Multivariate analysis using Backward LR logistic regression model showed significant results on GFAP with adjusted OR=15.629 (1.697-143.906) with P=0.015. This study demonstrated that GFAP and FABP-2 were significantly associated with the incidence of NEC. This may explain the pathogenesis of NEC through a hypoxic mechanism.

CCS CONCEPTS

• **Applied computing**; • **Health informatics**;

KEYWORDS

necrotizing enterocolitis, hypoxia, preterm

ACM Reference Format:
Dina Angelika, Risa Etika, and I Dewa Gede Ugrasena. 2022. Mechanism of necrotizing enterocolitis in preterm infants through the hypoxia signaling pathway, neuronal-glial signaling pathway, and intestinal fatty acid signaling pathway. In *2022 6th International Conference on Medical and Health Informatics (ICMHI 2022), May 13–15, 2022, Virtual Event, Japan.* ACM, New York, NY, USA, 4 pages. https://doi.org/10.1145/3545729.3545767

ICMHI 2022, May 13–15, 2022, Virtual Event, Japan

ACM ISBN 978-1-4503-9630-1/22/05…$15.00
https://doi.org/10.1145/3545729.3545767

1 INTRODUCTION

Preterm birth has a major contribution to death in children under five years of age worldwide. It is estimated that every year, 11% of all deliveries in the world are preterm, and one million out of six million preterm infant deaths are caused by complications of prematurity [1]. Necrotizing enterocolitis (NEC) is a digestive tract emergency that often occurs in preterm infants and often requires surgery [2]. NEC mortality is quite high, ranging from 15-40% and it is possible to reach 50% in developing countries [3]. Symptoms of sequelae of surviving NEC infants include short bowel syndrome, failure to thrive, and neurodevelopmental disorders [4]. Since clinical manifestations of NEC were observed in 1965, mortality and morbidity of NEC are still high [5]. The pathogenesis of NEC is still not fully elucidated and requires continuous research developments. However, some studies have demonstrated an association between hypoxia and NEC [6].

Previous studies have demonstrated that activation of hypoxia inducible factor-1 (HIF-1) is required for intestinal injury [7]. HIF-1alpha can be detected in the intestinal tissue of infants with NEC [8]. Hypoxia can affect the structure and function of the fetal gut where it will inhibit the adaptation of the newborn's digestive tract and increase the risk of NEC [9]. An increase in HIF-1alpha can be found in the umbilical blood of premature infants, which indicates that the baby is hypoxic [10]. Hypoxia causes brain damage and results in glial cell death which is characterized by an increase in glial fibrillary acidic protein (GFAP). GFAP is known to have high accuracy in detecting perinatal asphyxia where increased GFAP levels correlate with the severity of asphyxia [11]. Another study showed a decrease in the number of glial cells in vitro (expressed by GFAP) in NEC. This proves that there is damage to the intestinal nervous system in NEC which is correlated with brain nerve damage [12]. Glial derived neurotrophic factor (GDNF) signals are expressed

in peripheral glial cells [13]. GDNF activation can inhibit intestinal glial cell apoptosis and can inhibit the increase in intestinal permeability. The role of GDNF is to preserve the integrity of the intestinal epithelium and inhibit the inflammatory process including inhibiting the occurrence of NEC [14]. Fatty acid binding protein-2 (FABP-2) is found on the cell membrane of enterocytes, has a role in fat transport, and has a small molecular mass, so it is easy to move into the circulation if there is intestinal damage. Besides being used to detect NEC, FABP-2 can predict the extent of the severity of intestinal damage in NEC with fairly good accuracy [2, 3]. Peroxime proliferator activated receptor-gamma (PPAR-gamma) is a transcriptional gene in fat metabolism. An in vitro study found that intestinal ischemia can stimulate PPAR-gamma; however, activation of PPAR-gamma is required to repair intestinal damage in NEC [15]. Cytokines in the adaptive immune response are believed to have key roles in the NEC mechanism, including interleukin-6 (IL-6) and interleukin-8 (IL-8) [16]. IL-6 levels were detected to be elevated in preterm infants where this increase was correlated with a lower Apgar score. Increased levels of IL-6 were also detected to be associated with the incidence of NEC [17]. Furthermore, IL-8 RNA expression is also known to be increased in gut resection of infants experienced NEC [18].

The results of the above study indicate that the association between HIF-1alpha, GFAP, GDNF, FABP-2, PPAR-gamma, IL-6, and IL-8 can explain the pathogenesis of NEC through hypoxic mechanisms. This study aims to analyze the mechanism of the occurrence of NEC involving the roles of HIF-1alpha, GFAP, GDNF, FABP-2, PPAR-gamma, IL-6, and IL-8.

2 METHODS

This research design was an observational study. The sample of this study used preterm infants with gestational age <34 weeks or birth weight <1500 grams. Infants will be observed since birth until 2 weeks of age. Exclusion criteria were infants with intestinal atresia, spontaneous intestinal perforation, and sepsis. Research ethics were obtained from the Health Research Ethics Committee, Faculty of Medicine, Universitas Airlangga, Soetomo Academic General Hospital (Reference number. 0123/KEPK/I/2021). Informed and signed consent was acquired from the parents or authorized representatives of each infant.

At the time the infant was born, shortly after the umbilical cord is removed by the doctor, the placenta will be placed in a sterile container. Subsequently, blood collection was performed on the umbilical cord of the placenta. The volume of blood taken was 1 mL for examination of HIF-1alpha, GFAP, GDNF, FABP-2, PPAR-gamma, IL-6, and IL-8 (referred to as the first sample). Examination of HIF-1alpha, GFAP, GDNF, FABP-2, PPAR-gamma, IL-6, and IL-8 was repeated in infants with NEC symptoms using peripheral venous blood specimen with a blood volume of 1 mL (referred to as the second sample). Samples were examined using the enzyme-linked immunosorbent assay method (Elabscience Biotechnology; Texas, United States). Abdominal X-ray examination was performed on infants who showed symptoms of NEC. Biomarker and radiological examinations are carried out by competent specialists.

Infants were diagnosed as NEC if gastrointestinal symptoms were found (abdominal distension, vomiting, increased gastric aspirate >20%, bloody stools, abdominal tenderness) and abnormal abdominal radiographs (dilated bowel, ileus, ascites, pneumatosis intestinalis, persistent bowel loops, portal venous gas, pneumoperitoneum). The association between HIF-1alpha, GFAP, GDNF, FABP-2, PPAR-gamma, IL-6, and IL-8 on the incidence of NEC was analyzed statistically.

3 RESULTS

A total of 35 infants met the inclusion criteria of the study, however, there were 5 samples that could not be analyzed due to defects so that as many as 30 infants were included in the final analysis. Of the 30 infants, there were 9 (30%) infants who experienced NEC. Most of the infants with NEC were male, gestational age 30-<34 weeks, birth weight 1000-<1500 grams, and had a history of cesarean delivery. The group of infants with NEC had a minimum gestational age of 27 weeks, a maximum of 33 weeks, a mean of 30 weeks, and a standard deviation (SD) of 2.4 weeks. The group of infants with NEC also had a minimum birth weight of 950 grams, a maximum of 1450 grams, an average of 1116 grams, and an SD of 183.7 grams. All NEC infants in this study were singleton pregnancies. All infants with NEC also had a history of asphyxia at birth. A total of 2 out of 9 infants (22.2%) with NEC died. The onset of NEC was seen on average at 10 days of age, minimum 7 days, maximum 12 days, with SD of 1.5 days. The distribution of biomarker was described in table 1. There was no significant difference in the levels of biomarkers in the first and second samples (P>0.05).

Univariate analysis using logistic regression test showed significant results on GFAP with Odds Ratio (OR)=15.629 (95% confidence interval=1.697-143.906) P=0.015 and FABP-2 with OR=1.008 (1.001-1.015) P=0.033. Multivariate analysis using Backward LR logistic regression model showed significant results on GFAP with adjusted OR=15,629 (1,697-143.906) P=0,015. Figure 1 showed the receiver operator characteristic (ROC) curve between GFAP and the incidence of NEC. From the figure, the area under curve = 0.783 (0.573-0.993) with P value=0.015. The cut-off level of GFAP = 0.95 ng/mL has a sensitivity of 66.7% and a specificity of 95.2%.

4 DISCUSSION

Our study found that the majority of NEC occurred at 30-<34 weeks' gestation and birth weight of 1000-<1500 g. Similar studies reported that NEC occurred mostly in infants <34 weeks or birth weight <1500 grams, or even lower. The incidence of NEC can occur in term infants, which is around 7-25% or 0.05 cases per 1000 live births. The occurrence of NEC in term infants is usually related with a history of asphyxia and congenital abnormalities of the heart, gastrointestinal, and nervous organs.

In this study, 2 out of 9 infants (22.2%) with NEC died. Previous studies stated that NEC mortality is still quite high, ranging from 15-40% and could be higher in developing countries. NEC mortality increases at high NEC grades (grade 3) and at very low gestational ages. The use of ventilators, unavailability of pediatric surgeons, and the presence of sepsis increase NEC mortality [19].

Our study analyzed the significance of the association between HIF-1alpha, GFAP, GDNF, FABP-2, PPAR-gamma, IL-6, and IL-8

Table 1: Distribution of biomarkers in preterm infants with NEC and without NEC

Biomarker(unit)	With NEC (n=9)				Without NEC (n=21)			
	Minimum	Maximum	Mean	SD	Minimum	Maximum	Mean	SD
HIF-1alpha (ng/mL)								
First sample	1.10	10.50	3.31	3.08	0.90	2.70	1.32	0.41
Second sample	0.70	8.00	3.26	2.44	N/A	N/A	N/A	N/A
GFAP (ng/mL)								
First sample	0.20	6.50	2.00	2.25	0.10	1.30	0.38	0.27
Second sample	0.30	3.10	1.74	1.29	N/A	N/A	N/A	N/A
GDNF (ng/mL)								
First sample	1.05	14.11	4.39	4.19	1.07	3.48	1.69	0.56
Second sample	0.56	10.30	3.94	3.26	N/A	N/A	N/A	N/A
FABP-2 (ng/L)								
First sample	278.40	2207.00	844.44	677.04	211.40	597.50	335.48	104.39
Second sample	179.20	1571.00	807.37	534.03	N/A	N/A	N/A	N/A
PPAR-gamma (ng/mL)								
First sample	23.40	207.10	66.74	61.44	21.30	45.70	27.57	5.98
Second sample	8.80	142.30	63.23	45.62	N/A	N/A	N/A	N/A
IL-8 (ng/L)								
First sample	45.30	683.80	216.58	233.33	42.30	112.70	60.18	17.29
Second sample	39.60	504.60	218.46	159.54	N/A	N/A	N/A	N/A
IL-6 (ng/L)								
First sample	8.00	247.60	81.31	92.12	0.10	61.20	13.63	12.97
Second sample	13.60	495.50	113.71	151.28	N/A	N/A	N/A	N/A

N/A, not available

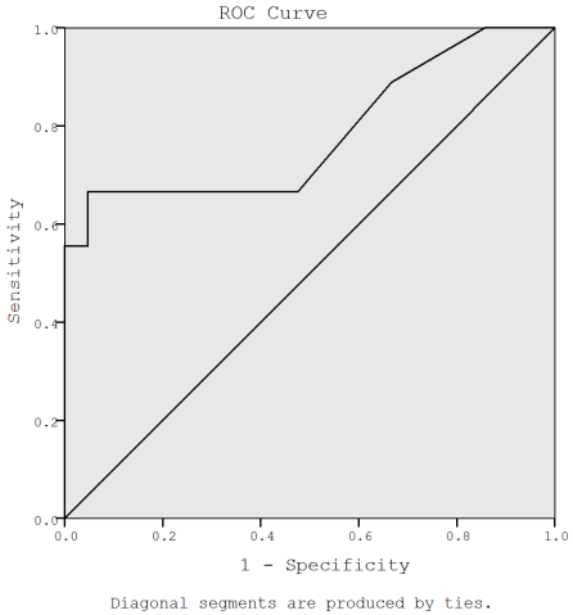

Figure 1: ROC curve between GFAP and the incidence of NEC

with the incidence of NEC. The results of statistical analysis showed significant results on GFAP and FABP-2. GFAP is a protein encoded by the human GFAP gene and belongs to the type III intermediate filament (IF) protein. Type III IF protein forms the cytoskeleton structure of muscle, brain, and mesenchymal tissue. GFAP is immediately released into the circulation when there is damage or death of astroglial cells [20]. Other studies have shown that an increase in GFAP is present from birth and correlates with the severity of asphyxia. The increase in GFAP can last up to 96 hours after the baby is born [11]. There is a new evidence that enteric glia participated actively in gut pathology associated with barrier dysfunction. Changes in intestinal permeability contribute to the pathology of NEC. There is a relationship between neuronal cell death and decreased GFAP expression in NEC [21].

A systematic review study conducted by Cheng in 2015 showed that FABP-2 examination has high accuracy in the diagnosis of NEC where accuracy increases according to the severity of NEC [3]. Apart from being a diagnostic tool, FABP-2 can be used as a tool to predict disease severity. FABP-2 can predict NEC cases that require surgery and which do not require surgery [22]. Other studies have also demonstrated that FABP-2 can be used to predict the extent of intestinal damage severity in NEC [23].

5 CONCLUSION

This study demonstrated that GFAP and FABP-2 were significantly associated with the incidence of NEC. This may explain the pathogenesis of NEC through hypoxic mechanisms, particularly in hypoxia associated with brain damage. The limitation of this study is that it does not consider maternal factors, therefore further research is needed.

6 FUTURE WORK

Cord blood has an abundance of immunomodulatory molecules that provide early information regarding efforts to diminish intestinal injury, primarily through hypoxic mechanisms. In the future, we would like to explore the potential mechanisms of which cord blood immunomodulatory molecules can be used to reduce NEC.

REFERENCES

[1] Qian, T., Zhang, R., Zhu, L., Shi, P., Yang, J., Yang, C. yi, Chen, D. mei, Shi, J. yun, Zhou, X. guang, Qiu, Y. ping, Yang, Y., He, L., He, S. ru, Cao, Y. tao, Wei, Q. fen, Kumar, M., Chen, C., 2017. Necrotizing enterocolitis in low birth weight infants in China: Mortality risk factors expressed by birth weight categories. Pediatr. Neonatol. 58, 509–515. doi: 10.1016/j.pedneo.2016.10.004.

[2] Chu, A., Hageman, J.R., Caplan, M.S., 2013. Necrotizing enterocolitis: Predictive markers and preventive strategies. Neoreviews 14, 113–120. DOI: 10.1542/neo.14-3-e113

[3] Cheng, S., Yu, J., Zhou, M., Tu, Y., Lu, Q., 2015. Serologic Intestinal-Fatty Acid Binding Protein in Necrotizing Enterocolitis Diagnosis: A Meta-Analysis. Biomed Res. Int. 2015, 1–8. doi: 10.1155/2015/156704. Epub 2015 Dec 22.

[4] Allendorf, A., Dewitz, R., Weber, J., Bakthiar, S., Schloesser, R., Rolle, U., 2018. Necrotizing enterocolitis as a prognostic factor for the neurodevelopmental outcome of preterm infants - match control study after 2 years. J. Pediatr. Surg. 53, 1573–1577. doi: 10.1016/j.jpedsurg.2018.01.006.

[5] Mizrahi, A., Barlow, O., Berdon, W., Blanc, WA., Silverman, W.A., 1965. Necrotizing enterocolitis in premature infants. J Pediatr. Apr;66:697-705. doi: 10.1016/s0022-3476(65)80003-8.

[6] Afrazi, A., Sodhi, C.P., Richardson, W., Neal, M., Good, M., Siggers, R., Hackam, D.J., 2011. New Insights Into the Pathogenesis and Treatment of Necrotizing Enterocolitis: Toll-Like Receptors and Beyond. Pediatr. Res. 69, 183–188. doi: 10.1203/PDR.0b013e3182093280.

[7] Feinman, R., Deitch, E.A., Watkins, A.C., Abungu, B., Colorado, I., Kannan, K.B., Sheth, S.U., Caputo, F.J., Lu, Q., Ramanathan, M., Attan, S., Badami, C.D., Doucet, D., Barlos, D., Bosch-Marce, M., Semenza, G.L., Xu, D.Z., 2010. HIF-1 mediates pathogenic inflammatory responses to intestinal ischemia-reperfusion injury. Am. J. Physiol. - Gastrointest. Liver Physiol. 299. doi: 10.1152/ajpgi.00065.2010. Epub 2010 Aug 5.

[8] Chen, Y., Chang, K.T.E., Lian, D.W.Q., Lu, H., Roy, S., Laksmi, N.K., Low, Y., Krishnaswamy, G., Pierro, A., Ong, C.C.P., 2016. The role of ischemia in necrotizing enterocolitis. J. Pediatr. Surg. 51, 1255–1261. doi: 10.1016/j.jpedsurg.2015.12.015. Epub 2016 Jan 8.

[9] Ferenc, K., Pietrzak, P., Godlewski, M.M., Piwowarski, J., Kilianczyk, R., Guilloteau, P., Zabielski, R., 2014. Intrauterine growth retarded piglet as a model for humans - Studies on the perinatal development of the gut structure and function. Reprod. Biol. 14, 51–60. doi: 10.1016/j.repbio.2014.01.005.

[10] Park, M.R., Park, J.Y., Kwon, D.N., Cho, S.G., Park, C., Seo, H.G., Ko, Y.G., Gurunathan, S., Kim, J.H., 2013. Altered protein profiles in human umbilical cords with preterm and full-term delivery. Electrophoresis. Feb;34(4):493-500. doi: 10.1002/elps.201200197.

[11] Chalak, L.F., Sánchez, P.J., Adams-Huet, B., Laptook, A.R., Heyne, R.J., Rosenfeld, C.R., 2014. Biomarkers for severity of neonatal hypoxic-ischemic encephalopathy and outcomes in newborns receiving hypothermia therapy. J. Pediatr. 164, 1–8. doi: 10.1016/j.jpeds.2013.10.067. Epub 2013 Dec 12.

[12] Zhou, Y., Yang, J., Watkins, D.J., Boomer, L.A., Matthews, M.A., Su, Y., Besner, G.E., 2013. Enteric nervous system abnormalities are present in human necrotizing enterocolitis: Potential neurotransplantation therapy. Stem Cell Res. Ther. 4(6):157. doi: 10.1186/scrt387.

[13] Uesaka, T., Young, H.M., Pachnis, V., Enomoto H., 2016. Development of the intrinsic and extrinsic innervation of the gut. Dev Biol. Sep 15;417(2):158-67. doi: 10.1016/j.ydbio.2016.04.016. Epub 2016 Apr 22.

[14] Zhang, D.K., He, F.Q., Li, T.K., Pang, X.H., Cui, D. J., Xie, Q., Li, X.H., Gan, H.T., 2010. Glial-derived neurotrophic factor regulates intestinal epithelial barrier function and inflammation and is therapeutic for murine colitis. J Pathol. 2010 Oct;222(2):213-22. J Pathol. Oct;222(2):213-22. doi: 10.1002/path.2749.

[15] Baregamian, N., Mourot, J.M., Ballard, A.R., Evers, B.M., Chung, D.H., 2009. PPAR-gamma agonist protects against intestinal injury during necrotizing enterocolitis. Biochem Biophys Res Commun. Feb 6;379(2):423-7. doi: 10.1016/j.bbrc.2008.11.155. Epub 2008 Dec 27.

[16] Tremblay, É., Thibault, M.P., Ferretti, E., Babakissa, C., Bertelle, V., Bettolli, M., Burghardt, K.M., Colombani, J.F., Grynspan, D., Levy, E., Lu, P., Mayer, S., Ménard, D., Mouterde, O., Renes, I.B., Seidman, E.G., Beaulieu, J.F., 2016. Gene expression profiling in necrotizing enterocolitis reveals pathways common to those reported in Crohn's disease. BMC Med. Genomics 9, 1–12. doi: 10.1186/s12920-016-0166-9.

[17] Arad, I., Bar-Oz, B., Ergaz, Z., Nir, A., Barak, V. 2010. Interleukin-6 and N-terminal pro-brain natriuretic peptide cord blood levels in premature infants: correlations with perinatal variables. Isr Med Assoc J. Jul;12(7):419-23. PMID: 20862823

[18] Nadler, E.P., Stanford, A., Zhang, X.R., Schall, L.C., Alber, S.M., Watkins, S.C., Ford, H.R., 2001. Intestinal cytokine gene expression in infants with acute necrotizing enterocolitis: Interleukin-11 mRNA expression inversely correlates with extent of disease. J. Pediatr. Surg. 36, 1122–1129. doi: 10.1053/jpsu.2001.25726.

[19] Gephart, S.M., McGrath, J.M., Effken, J.A., Halpern, M.D., 2012. Necrotizing enterocolitis risk state of the science. Adv. Neonatal Care 12, 77–87. doi: 10.1097/ANC.0b013e31824cee94.

[20] Satriano, A., Pluchinotta, F., Gazzolo, F., Serpero, L., Gazzolo, D., 2017. The potentials and limitations of neuro-biomarkers as predictors of outcome in neonates with birth asphyxia. Early Hum. Dev. 105, 63–67. doi: 10.1016/j.earlhumdev.2016.12.005. Epub 2016 Dec 18.

[21] Savidge TC, Sofroniew MV, Neunlist M. Starring roles for astroglia in barrier pathologies of gut and brain. Lab Invest. 2007 Aug;87(8):731-6. doi: 10.1038/labinvest.3700600. Epub 2007 Jul 2.

[22] Ng, E.W.Y., Poon, T.C.W., Lam, H.S., Cheung, H.M., Ma, T.P.Y., Chan, K.Y.Y., Wong, R.P.O., Leung, K.T., Lam, M.M.T., Li, K., Ng, P.C., 2013. Gut-associated biomarkers L-FABP, I-FABP, and TFF3 and LIT score for diagnosis of surgical necrotizing enterocolitis in preterm infants. Ann. Surg. 258, 1111–1118. doi: 10.1097/SLA.0b013e318288ea96.

[23] Evennett, N.J., Hall, N.J., Pierro, A., Eaton, S., 2010. Urinary intestinal fatty acid-binding protein concentration predicts extent of disease in necrotizing enterocolitis. J. Pediatr. Surg. 45, 735–740. doi: 10.1016/j.jpedsurg.2009.09.024.

Mechanism of necrotizing enterocolitis in preterm infants through the hypoxia signaling pathway, neuronal-glial signaling pathway, and intestinal fatty acid signaling pathway

ORIGINALITY REPORT

18%	14%	15%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	doaj.org Internet Source	2%
2	hal.archives-ouvertes.fr Internet Source	2%
3	www.thieme-connect.com Internet Source	1%
4	Dina Angelika, I. Dewa Gede Ugrasena, Risa Etika, Paulus Rahardjo, Arend F. Bos, Pieter J.J. Sauer. "The incidence of osteopenia of prematurity in preterm infants without phosphate supplementation", Medicine, 2021 Publication	1%
5	assets.researchsquare.com Internet Source	1%
6	Alex C. Williams, Harmanpreet Kaur, Shamsi Iqbal, Ryen W. White, Jaime Teevan, Adam Fourney. "Mercury", Proceedings of the 32nd	1%

Annual ACM Symposium on User Interface Software and Technology, 2019
Publication

7	e-journal.unair.ac.id Internet Source	1 %
8	Biesterbos, Jacqueline W. H., Gwendolyn Beckmann, Rob B. M. Anzion et al. "Sensitive Method for Quantification of Octamethylcyclotetrasiloxane (D4) and Decamethylcyclopentasiloxane (D5) in End-Exhaled Air by Thermal Desorption Gas Chromatography Mass Spectrometry", Analytical Chemistry Publication	1 %
9	Lukas Reithmeier, Oliver Krauss, Gerald Adam Zwettler. "Transfer Learning and Hyperparameter Optimization for Instance Segmentation with RGB-D Images in Reflective Elevator Environments", University of West Bohemia, 2021 Publication	1 %
10	cris.maastrichtuniversity.nl Internet Source	1 %
11	Aamer Imdad, Faseeha Rehman, Evans Davis, Deepika Ranjit et al. "Effects of neonatal nutrition interventions on neonatal mortality and child health and development outcomes: A systematic review", Campbell Systematic	1 %

Reviews, 2021
Publication

12	pure.rug.nl Internet Source	1 %
13	core.ac.uk Internet Source	1 %
14	Abdulelah AlQahtani, Yousef Al-Dlaigan, Ahmed Almahdy. "Microtensile Bond Strength of Bioactive Pit and Fissure Sealants Bonded to Primary and Permanent Teeth", Materials, 2022 Publication	<1 %
15	repository.unair.ac.id Internet Source	<1 %
16	Yaqian Wang, Seyedeh Maryam Seyed Barghi, Yanhong Yang, Reza Akhavan-Sigari. "Value of HSP90α in Lung Cancer Diagnosis and Recurrence Prediction: A Cohort Study", Oncology Research and Treatment, 2021 Publication	<1 %
17	Chan, Kathy Yuen Yee, Fiona Wan Lun Leung, Hugh Simon Lam, Yuk Him Tam, Ka Fai To, Hon Ming Cheung, Kam Tong Leung, Terence Chuen Wai Poon, Kim Hung Lee, Karen Li, Tai Fai Fok, and Pak Cheung Ng. "Immunoregulatory Protein Profiles of Necrotizing Enterocolitis versus Spontaneous	<1 %

Intestinal Perforation in Preterm Infants", PLoS ONE, 2012.
Publication

18	Ryuta Saka, Tetsu Wakimoto, Fumiko Nishiumi, Takashi Sasaki et al. "Surfactant protein-D attenuates the lipopolysaccharide-induced inflammation in human intestinal cells overexpressing toll-like receptor 4", Pediatric Surgery International, 2015 Publication	<1 %
19	hal-imt.archives-ouvertes.fr Internet Source	<1 %
20	Catharina J.M. Frijns, Gabriël J.E. Rinkel, Domenico Castigliego, Jan van Gijn, Jan J. Sixma, Rob Fijnheer. "Endothelial Cell Activation after Subarachnoid Hemorrhage", Neurosurgery, 2002 Publication	<1 %
21	Dina Angelika, Risa Etika, Angelica Diana Vita, Setya Mithra, I Dewa Gede Ugrasena. "Necrotizing Enterocolitis in Preterm Infants Born to Mother with COVID-19", Open Access Macedonian Journal of Medical Sciences, 2021 Publication	<1 %
22	referencecitationanalysis.com Internet Source	<1 %

23	Dina Angelika, Risa Etika, Naomi Nathania Kusumawardani, Setya Mithra, I Dewa Gede Ugrasena. "Observational study on necrotizing enterocolitis in neonates born to SARS-CoV-2-positive mothers", Annals of Medicine and Surgery, 2022 Publication	<1 %
24	Jeffrey C. Chan, Jeffery Sobal. "Family meals and body weight. Analysis of multiple family members in family units", Appetite, 2011 Publication	<1 %
25	journals.lww.com Internet Source	<1 %
26	static.frontiersin.org Internet Source	<1 %
27	www.biorxiv.org Internet Source	<1 %
28	www.science.gov Internet Source	<1 %
29	Alexia Gomart, Alexandre Vallée, Yves Lecarpentier. "Necrotizing Enterocolitis: LPS/TLR4-Induced Crosstalk Between Canonical TGF-β/Wnt/β-Catenin Pathways and PPARγ", Frontiers in Pediatrics, 2021 Publication	<1 %

30	Dewi Anggraini, Dewi Santosaningsih, Pepy Dwi Endraswari, Novira Jasmin, Fajri Marindra Siregar, Usman Hadi, Kuntaman Kuntaman. "Multicenter Study of the Risk Factors and Outcomes of Bloodstream Infections Caused by Carbapenem-Non-Susceptible Acinetobacter baumannii in Indonesia", Tropical Medicine and Infectious Disease, 2022 Publication	<1 %
31	www.ssoar.info Internet Source	<1 %
32	"Neonatology", Springer Science and Business Media LLC, 2018 Publication	<1 %
33	Keeling s Fetal and Neonatal Pathology, 2015. Publication	<1 %

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Mechanism of necrotizing enterocolitis in preterm infants through the hypoxia signaling pathway, neuronal-glial signaling pathway, and intestinal fatty acid signaling pathway

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4