Advances in Clinical Medicine 临床医学进展, 2023, 13(3), 4095-4102
Published Online March 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.133588

Hans汉斯

早产儿与新生儿坏死性小肠结肠炎的现状与预防措施

贺泽博[1,2,3]，康　权[1,2,3*]

[1]重庆医科大学附属儿童医院普外创伤外科，重庆
[2]国家儿童健康与疾病临床医学研究中心，重庆
[3]儿童发育疾病研究教育部重点实验室，重庆

收稿日期：2023年2月17日；录用日期：2023年3月13日；发布日期：2023年3月21日

摘　要

坏死性小肠结肠炎(NEC)是早产儿和新生儿常见的胃肠道危重病，有着较高的发病率和病死率。本文基于目前国内外相关研究，旨在为NEC的诊断、防治以及预防提供证据和参考。预防NEC的措施应及早考虑，如母乳喂养或用母乳银行提供的经巴氏杀菌的人类供者母乳进行营养，服用益生菌，避免使用组胺II受体拮抗剂，以及限制性抗生素治疗。

关键词

坏死性小肠结肠炎，新生儿，母乳，益生菌

Prevention and Research State of Necrotizing Enterocolitis in Premature Infants and Newborns

Zebo He[1,2,3], Quan Kang[1,2,3*]

[1]Department of General Surgery, Children's Hospital of Chongqing Medical University, Chongqing
[2]National Clinical Research Center for Child Health and Disorders, Chongqing
[3]Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing

Received: Feb. 17th, 2023; accepted: Mar. 13th, 2023; published: Mar. 21st, 2023

*通讯作者。

文章引用：贺泽博，康权．早产儿与新生儿坏死性小肠结肠炎的现状与预防措施[J]．临床医学进展，2023，13(3): 4095-4102. DOI: 10.12677/acm.2023.133588

Abstract

Necrotizing enterocolitis (NEC) is a devastating gastrointestinal disease of neonates and preterm infants, with high morbidity and mortality. To provide Prevention and research state for management of NEC, this article is based on the current domestic and overseas studies.

Keywords

Necrotizing Enterocolitis, Neonate, Breast Milk, Probiotics

1. 引言

坏死性小肠结肠炎(necrotizing enterocolitis, NEC)是影响早产儿和新生儿胃肠道的常见的危重疾病。NEC 的特征是肠壁各层都有出血性和坏死性炎症。临床通常根据 NEC 的 Bell 分期标准对炎症进行分类，产气菌从胃肠腔进入肠壁在该病的病理生理学中起着重要作用。NEC 的早期临床症状通常是多样化和非特异性的。最初很难区分 NEC 和食物不耐受，这在早产儿以及其他胃肠道疾病以及脓毒症中相当常见。

2. 流行病学

据国外研究报道报道，NEC 的发病率为每 1000 名活产儿中有 1~3 名，而小于 1500 g 的早产儿的发病率可能达到 7% [1] [2]。据报道，在体重在 400 克到 750 克之间的极低出生体重儿(ELBW)中，NEC 的发病率为 14%，而在 1251 克到 1500 克到 3%的极低出生体重儿(VLBW)中，NEC 的发病率下降了 3% [3]。2018 年我国的一篇调查研究结果显示，NEC 在我国极低出生体质量(very low birth weight, VLBW)早产儿中的发病率高达 5.6% [4]。

3. 危险因素和发病机制

NEC 与多种危险因素有关，早产儿最有可能是由于胃肠道发育不成熟。足月新生儿的 NEC 通常与其他病理情况有关，如先天性心脏病、呼吸功能不全、败血症、新生儿癫痫、低血糖、严重的宫内发育迟缓、红细胞增多症、腹裂和先天性疱疹感染[5] [6] [7] [8]。血流动力学不稳定，红细胞输注[9] [10]，缺氧和缺血，以及低温和发热[6] [11]，口服高渗药物溶液和组胺 II 受体拮抗剂的使用，可以中和胃酸的保护作用，允许异常细菌在胃肠道积聚，也被描述为 NEC 发生的危险因素[12] [13]。在这方面，过度和长期使用抗生素仍然是有争议的[14]。配方喂养也被描述为 NEC 发展的一个危险因素[15] [16]。所有患有 NEC 的儿童中，有 90%在出生后的第一天就服用过配方奶[17]。新生儿肠道细菌定植具有免疫调节功能，一般由母乳促进。母乳喂养新生儿肠道的定植(双歧杆菌和肠道细菌)不同于配方奶新生儿(双歧杆菌种类少于母乳喂养的新生儿，大肠杆菌，艰难梭菌，类杆菌，普雷沃特氏菌，乳杆菌) [18]。

乳杆菌和双歧杆菌可以直接影响肠道上皮屏障功能[19] [20] [21] [22]。因此，细菌肠道定植中断被认为是发生 NEC 的潜在危险因素[18]。NEC 的进一步危险因素可能是肠内喂养的时机和初始容量率、喂养进度和肠内喂养的选择。研究表明，与出生 72 小时后延迟喂养相比，小于 1500 克的早产儿在 48 小时内

提前喂养在缩短体重增加时间、缩短肠外营养持续时间和减少住院时间方面更有好处[23]。因此，早期喂养似乎对新生儿更有利，与延迟喂养相比，患 NEC 的机会并没有增加。为早产儿提供初始肠道容积率有多种策略，例如在生命的第一周，每天以 15~20 ml/kg 母乳或配方奶粉每天 15~20 ml/kg 的微量或营养性喂养[24]，或者从每天 20~30 ml/kg 开始提前喂养，然后每天增加 20~30 ml/kg，达到每天 140~150 ml/kg [25] [26]。

然而，国外的研究对此也有不同意见，例如，国外的一篇循证医学综述认为没有证据表明早期营养喂养与肠道禁食相比可以阻止 NEC [27]，也有一篇随机对照研究认为提前喂养与 NEC 的发病率更高有关[26]。但其他相关试验没有发现类似的积极肠内喂养策略导致的 NEC 发生率更高[28] [29] [30]。

4. 临床表现

NEC 的临床表现较为离散，可表现为非特异性全身症状如皮肤花白、心率增快、体温不升、发热、易激惹、嗜睡，亦可为典型的腹胀、喂养残留、便血、呕吐、呕血、肠鸣音差/腹部包块等胃肠道症状，也有较为少见的循环呼吸系统症状如呼吸暂停、心动过缓、血氧波动、低血压等。早产儿与足月儿临床表现也存在差异，早产儿发病大多以呼吸暂停、反应差等全身感染中毒症状为首发表现，腹胀、肠鸣音减弱亦较常见，而典型的 NEC 三联征的呕吐、腹泻、血便一般出现较晚。足月儿 NEC 发病时间较早产儿早，主要以典型的胃肠道症状为主，如腹胀、呕吐、血便，但全身症状表现较早产儿轻，肠穿孔发病率较早产儿低[31]。

5. 诊断程序

疾病过程中由于炎症过程中血小板和粒细胞丢失，血细胞计数通常显示血小板减少和白细胞减少。炎症标志物 IL-6 和 IL-8、降钙素原(PCT)和 C 反应蛋白(CRP)作为非特异性炎症参数在炎症过程中升高，血象结果与感染类似。由于液体置换到病变肠段或脓毒症伴发毛细血管渗漏综合征，患儿的血气分析(BGA)通常显示代谢性酸中毒[32] [33]。平片可用于诊断 NEC [34]，根据 Bell 分期的不同，包括正常腹部 X 光、肠扩张、肠梗阻、肠气肿、门静脉气体或气腹。和 X 光一样，腹部超声也可以显示门静脉气体和肠气肿，并且还能提供有关腹水、肠蠕动、肠壁厚度、肠血管和回声的信息[34]。

6. 治疗

NEC 采用保守对症治疗和外科手术干预。保守的对症治疗包括禁食、全肠外营养、鼻胃/口胃引流、液体平衡和止痛镇静。患病的儿童常见高血糖，因此需要限制葡萄糖的供应，必要时需要胰岛素治疗。由于严重的炎症，迅速而充分的纠正低血容量是至关重要的。在容量替代治疗期间，红细胞压积应保持在 30%至 40%之间。此外，为了稳定血压，除了容量替代治疗外，通常还需要儿茶酚胺(去甲肾上腺素、肾上腺素)。在患有 NEC 的儿童中，20%~30%可以发现菌血症。根据国外的研究结果，推荐经验性使用抗生素选择：万古霉素/庆大霉素/克林霉素、万古霉素/庆大霉素/甲硝唑或万古霉素/庆大霉素/哌拉西林[35] [36]。

除了保守治疗外，及时进行儿科手术也是至关重要的。出现有胃肠道穿孔伴气腹证据是手术的绝对适应症，手术的适应症还包括进行性血小板减少、肠管扩张、反复腹部扫描出现持续性肠环、门静脉内有气体迹象、腹壁红斑、对症治疗后，临床症状仍迅速恶化以及穿刺阳性。有关手术干预的决定应由新生儿科医生和儿科外科医生根据患儿情况作出。症状的严重程度和个体的临床情况以及婴儿的年龄在整个疾病过程中起着决定性的作用。必要时需进行剖腹手术，包括适当切除受影响的肠段和放置造口。一期腹膜引流可以作为开腹手术的替代疗法。在对 117 名体重 < 34 周的早产儿和 NEC 合并肠穿孔的多中

心对照研究中，不适当的腹腔引流和直接腹腔引流在死亡率上没有显著差异[37]。

7. 并发症

并发症可分为急性并发症，即发生在 NEC 诊断后的前几天内，以及远期并发症。急性并发症主要包括暴发性脓毒症合并脑膜炎、腹膜炎、局部脓肿、DIC，以及呼吸衰竭和低血压休克的呼吸和心血管并发症，66%的死亡病例发生在 NEC 确诊后的七天内。新生儿 NEC 致死结局的主要危险因素是未成熟、低出生体重和疾病的严重程度。高达 9%的患者可能会因为 NEC 影响整个胃肠道而发展为短肠综合征，从而导致肠衰竭。腹腔内肠梗阻和粘连发病率在 30%到 36%之间。据描述，NEC 与肠狭窄发生之间的延迟时间为 27.5 至 62 天(中位数为 34 天)。婴儿肠管狭窄的主要并发症包括肠穿孔、细菌败血症、严重电解质失衡、低蛋白血症、胆汁淤积和严重生长障碍[38]。患有需外科干预 NEC 以及晚期菌血症(出生后 2 周以上)的患儿，患脑瘫和小头畸形症的风险增加。而没有手术也没有菌血症的 NEC 婴儿没有增加发育障碍的风险[39]。

8. 预测

根据美国的研究结果，在新生儿重症监护室，NEC 的发病率为 2%~5%，其中极低出生体重(very low birth weight, VLBW)儿发病率为 4.5%~8.7%，病死率为 20%~30%，超低出生体重(extremely low birth weight, ELBW)儿病死率则高达 30%~50.9% [40] [41] [42]。

9. 预防

由于壁内炎症一般不能通过保守或手术治疗达到令人满意的程度，因此必须把预防 NEC 放在非常重要的位置。产前给予母体糖皮质激素已被证实在诱导肺成熟和预防 NEC 方面有积极作用。研究发现，单独用母乳喂养比用配方奶喂养患 NEC 的风险低 6~10 倍[43]。推荐早产儿延迟结扎脐带，研究发现，延迟结扎脐带可增加新生儿血容量，增加肠黏膜血供，减少肠黏膜缺血缺氧性损伤，从而降低早产儿 NEC 的发生率[44] [45]。推荐使用布洛芬关闭早产儿合并血流动力学改变的动脉导管未闭。

在喂养方面推荐，推荐首选亲母母乳喂养，当其不足或缺乏时，使用捐赠人乳替代母乳喂养。作为预防 NEC 的一种手段。美国儿科学会在 2012 年建议，所有新生儿，包括早产儿，都应该接受新鲜或冷冻的母乳，并适当添加蛋白质、矿物质和维生素，以确保最佳营养，特别是体重不到 1.5 公斤的婴儿。如果亲生母亲尽管做出了巨大的刺激努力，但没有产生母乳或只产生了极少量的母乳，或者禁止使用母乳，则使用捐赠人乳替代母乳喂养[46]。当然对捐赠者的母乳进行巴氏杀菌是必要的，以最大限度地减少疾病传播的风险，并使大多数病毒和细菌污染物失活。另一方面，巴氏杀菌会导致一些具有生物功能的牛奶成分的数量和/或活性的损失。即使在巴氏杀菌后，供体母乳依然比配方奶对婴儿更好。国外研究报告显示，与配方奶喂养相比，接受捐赠母乳的早产儿患 NEC 的风险降低了 2.77 倍[47]。

推荐按个体化原则添加母乳强化剂(human milk fortifier, HMF)，根据可获得性，选择人乳或牛乳来源的 HMF (human milk fortifier, HMF)。HMF 包含了多种营养素，在母乳中添加 HMF 可满足早产儿的生长发育需求，减少宫外发育迟缓。《早产儿母乳强化剂使用专家共识》建议，出生体重 ＜1800 g 的早产儿，母乳喂养量达 50~80 mL/(kg·d)时开始在母乳中添加 HMF [48]。《早产儿喂养不耐受临床诊疗指南(2020)》指出，添加 HMF 不会增加早产儿喂养不耐受(feeding intolerance, FI)的风险，推荐按个体化原则添加 HMF [49]。

国外研究指出：预防性补充益生菌与显著降低 NEC 发病率(风险比 0.55，95%可信区间)和死亡率(风险比 0.72，95%可信区间)有关，因此被推荐为预防措施[50]。

益生菌被世界卫生组织(WHO)定义为“活菌，当给予足够数量的益生菌时，会给宿主带来健康益处”[51]。通常使用的益生菌是乳酸菌，如乳杆菌和双歧杆菌[52]。研究表明，在早产儿中引入益生菌可能是有益的，因为它们能够改善肠道微生物群的多样性，防止病原体过度生长[53]。益生菌补充剂可以增加喂养耐受性，减少达到完全喂养的天数，并防止医院感染[54] [55]。益生菌的局部健康促进作用主要通过增加巨噬细胞的活性，提高杀伤细胞、T 细胞和干扰素的数量，抑制 IL-6、IL-8 等信号分子，增强粘膜免疫反应，并对抗病原微生物的定植和移位，从而整体改善肠道屏障的完整性和功能[56]-[61]。

避免长期的经验性抗生素治疗也与 NEC 发生率的降低有关[10]。国外有研究提出口服乳铁蛋白可以降低新生儿败血症和 NEC 的发生率，这意味着它可能被推荐作为未来的预防措施[62]。

10. 总结和结论

NEC 是早产儿和新生儿最常见的胃肠道获得性疾病，死亡率高。到目前为止，对 NEC 的病理生理机制还没有完全、详细地了解。NEC 根据改良的 Bell’s 分类进行分类，其特征是肠壁各层的炎症。治疗 NEC 可采取保守治疗和手术治疗。

最重要的预防措施包括母乳喂养(母乳或人类捐赠者母乳)、按个体化原则添加母乳强化剂、补充益生菌、避免使用组胺 II 型受体拮抗剂和限制性抗生素治疗。

参考文献

[1] Kosloske, A.M. (1994) Epidemiology of Necrotizing Enterocolitis. *Acta Paediatrica*, **83**, 2-7. https://doi.org/10.1111/j.1651-2227.1994.tb13232.x

[2] Horbar, J.D., Badger, G.J., Carpenter, J.H., *et al*. (2002) Trends in Mortality and Morbidity for Very Low Birth Weight Infants, 1991-1999. *Pediatrics*, **110**, 143-151. https://doi.org/10.1542/peds.110.1.143

[3] Lemons, J.A., Bauer, C.R., Oh, W., *et al*. (2001) Very Low Birth Weight Outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. *Pediatrics*, **107**, e1. https://doi.org/10.1542/peds.107.1.e1

[4] 中国新生儿重症监护室协作性质量改进研究协作组. 我国 25 家Ⅲ级新生儿重症监护病房极低出生体重儿出院结局的横断面调查[J]. 中华围产医学杂志, 2018, 21(6): 394-400.

[5] Lambert, D.K., Christensen, R.D., Henry, E., *et al*. (2007) Necrotizing Enterocolitis in Term Neonates: Data from a Multihospital Health-Care System. *Journal of Perinatology*, **27**, 437-443. https://doi.org/10.1038/sj.jp.7211738

[6] Short, S.S., Papillon, S., Berel, D., Ford, H.R., Frykman, P.K. and Kawaguchi, A. (2014) Late Onset of Necrotizing Enterocolitis in the Full-Term Infant is Associated with Increased Mortality: Results From a Two-Center Analysis. *Journal of Pediatric Surgery*, **49**, 950-953. https://doi.org/10.1016/j.jpedsurg.2014.01.028

[7] Ostlie, D.J., Spilde, T.L., St Peter, S.D., *et al*. (2003) Necrotizing Enterocolitis in Full-Term Infants. *Journal of Pediatric Surgery*, **38**, 1039-1042. https://doi.org/10.1016/S0022-3468(03)00187-8

[8] Hull, M.A., Fisher, J.G., Gutierrez, I.M., *et al*. (2014) Mortality and Management of Surgical Necrotizing Enterocolitis in Very Low Birth Weight Neonates: A Prospective Cohort Study. *Journal of the American College of Surgeons*, **218**, 1148-1155. https://doi.org/10.1016/j.jamcollsurg.2013.11.015

[9] Amin, S.C., Remon, J.I., Subbarao, G.C. and Maheshwari, A. (2012) Association between Red Cell Transfusions and Necrotizing Enterocolitis. *The Journal of Maternal-Fetal & Neonatal Medicine*, **25**, 85-89. https://doi.org/10.3109/14767058.2012.715465

[10] Cotton, C.M., Taylor, S., Stoll, B., Goldberg, R.N., Hansen, N.I., Sanchez, P.J., *et al*. (2009) Prolonged Duration of Initial Empirical Antibiotic Treatment is Associated with Increased Rates of Necrotizing Enterocolitis and Death for Extremely Low Birth Weight Infants. *Pediatrics*, **123**, 58-66. https://doi.org/10.1542/peds.2007-3423

[11] Lyu, Y., Shah, P.S., Ye, X.Y., *et al*. (2015) Association Between Admission Temperature and Mortality and Major Morbidity in Preterm Infants Born at Fewer Than 33 Weeks’ Gestation. *JAMA Pediatrics*, **169**, e150277. https://doi.org/10.1001/jamapediatrics.2015.0277

[12] Bilali, A., Galanis, P., Bartsocas, C., Sparos, L. and Velonakis, E. (2013) H2-Blocker Therapy and Incidence of Necrotizing Enterocolitis in Preterm Infants: A Case-Control Study. *Pediatrics and Neonatology*, **54**, 141-142. https://doi.org/10.1016/j.pedneo.2013.01.011

[13] Guillet, R., Stoll, B.J., Cotton, C.M., *et al*. (2006) Association of H2-Blocker Therapy and Higher Incidence of Necrotizing Enterocolitis in Very Low Birth Weight Infants. *Pediatrics*, **117**, e137-e142. https://doi.org/10.1542/peds.2005-1543

[14] Schulman, J., Dimand, R.J., Lee, H.C., Duenas, G.V., Bennett, M.V. and Gould, J.B. (2015) Neonatal Intensive Care Unit Antibiotic Use. *Pediatrics*, **135**, 826-833. https://doi.org/10.1542/peds.2014-3409

[15] Book, L.S., Herbst, J.J., Atherton, S.O. and Jung, A.L. (1975) Necrotizing Enterocolitis in Low-Birth-Weight Infants Fed an Elemental Formula. *The Journal of Pediatrics*, **87**, 602-605. https://doi.org/10.1016/S0022-3476(75)80835-3

[16] Good, M., Sodhi, C.P., Egan, C.E., *et al*. (2015) Breast Milk Protects Against the Development of Necrotizing Enterocolitis through Inhibition of Toll-Like Receptor 4 in the Intestinal Epithelium via Activation of the Epidermal Growth Factor Receptor. *Mucosal Immunology*, **8**, 1166-1179. https://doi.org/10.1038/mi.2015.30

[17] Berseth, C.L. (2005) Feeding Strategies and Necrotizing Enterocolitis. *Current Opinion in Pediatrics*, **17**, 170-173. https://doi.org/10.1097/01.mop.0000150566.50580.26

[18] Gritz, E.C. and Bhandari, V. (2015) The Human Neonatal Gut Microbiome: A Brief Review. *Frontiers in Pediatrics*, **3**, Article 17. https://doi.org/10.3389/fped.2015.00017

[19] Martin, R., Nauta, A.J., Ben Amor, K., Knippels, L.M., Knol, J. and Garssen, J. (2010) Early Life: Gut Microbiota and Immune Development in Infancy. *Beneficial Microbes*, **1**, 367-382. https://doi.org/10.3920/BM2010.0027

[20] García-Lafuente, A., Antolín, M., Guarner, F., Crespo, E. and Malagelada, J.R. (2001) Modulation of Colonic Barrier Function by the Composition of the Commensal Flora in the Rat. *Gut*, **48**, 503-507. https://doi.org/10.1136/gut.48.4.503

[21] Madsen, K., Cornish, A., Soper, P., *et al*. (2001) Probiotic Bacteria Enhance Murine and Human Intestinal Epithelial Barrier Function. *Gastroenterology*, **121**, 580-591. https://doi.org/10.1053/gast.2001.27224

[22] Parassol, N., Freitas, M., Thoreux, K., Dalmasso, G., Bourdet-Sicard, R. and Rampal, P. (2005) Lactobacillus casei DN-114 001 Inhibits the Increase in Paracellular Permeability of Enteropathogenic *Escherichia coli*-Infected T84 Cells. *Research in Microbiology*, **156**, 256-262. https://doi.org/10.1016/j.resmic.2004.09.013

[23] Sallakh-Niknezhad, A., Bashar-Hashemi, F., Satarzadeh, N., Ghojazadeh, M. and Sahnazarli, G. (2012) Early versus Late Trophic Feeding in Very Low Birth Weight Preterm Infants. *Iranian Journal of Pediatrics*, **22**, 171-176.

[24] Good, M., Sodhi, C.P. and Hackam, D.J. (2014) Evidence-Based Feeding Strategies before and after the Development of Necrotizing Enterocolitis. *Expert Review of Clinical Immunology*, **10**, 875-884. https://doi.org/10.1586/1744666X.2014.913481

[25] Kimak, K.S., de Castro Antunes, M.M., Braga, T.D., Brandt, K.G. and de Carvalho Lima, M. (2015) Influence of Enteral Nutrition on Occurrences of Necrotizing Enterocolitis in Very-Low-Birth-Weight Infants. *Journal of Pediatric Gastroenterology and Nutrition*, **61**, 445-450. https://doi.org/10.1097/MPG.0000000000000835

[26] Berseth, C.L., Bisquera, J.A. and Paje, V.U. (2003) Prolonging Small Feeding Volumes Early in Life Decreases the Incidence of Necrotizing Enterocolitis in Very Low Birth Weight Infants. *Pediatrics*, **111**, 529-534. https://doi.org/10.1542/peds.111.3.529

[27] Morgan, J., Bombell, S. and McGuire, W. (2013) Early Trophic Feeding versus Enteral Fasting for Very Preterm or Very Low Birth Weight Infants. *Cochrane Database of Systematic Reviews*, **3**, Article ID: CD000504. https://doi.org/10.1002/14651858.CD000504.pub4

[28] Kimak, K.S., de Castro Antunes, M.M., Braga, T.D., Brandt, K.G. and de Carvalho Lima, M. (2015) Influence of Enteral Nutrition on Occurrences of Necrotizing Enterocolitis in Very-Low-Birth-Weight Infants. *Journal of Pediatric Gastroenterology and Nutrition*, **61**, 445-450. https://doi.org/10.1097/MPG.0000000000000835

[29] Caple, J., Armentrout, D., Huseby, V., *et al*. (2004) Randomized, Controlled Trial of Slow versus Rapid Feeding Volume Advancement in Preterm Infants. *Pediatrics*, **114**, 1597-600. https://doi.org/10.1542/peds.2004-1232

[30] Salhotra, A. and Ramji, S. (2004) Slow versus Fast Enteral Feed Advancement in Very Low Birth Weight Infants: A Randomized Control Trial. *Indian Pediatrics*, **41**, 435-441.

[31] 梅杰. 365 例新生儿坏死性小肠结肠炎的临床分析[D]: [硕士学位论文]. 长春: 吉林大学, 2020. 10.27162/d.cnki.gjlin.2020.004391

[32] Kenton, A.B., O'Donovan, D., Cass, D.L., *et al*. (2005) Severe Thrombocytopenia Predicts Outcome in Neonates with Necrotizing Enterocolitis. *Journal of Perinatology*, **25**, 14-20. https://doi.org/10.1038/sj.jp.7211180

[33] Hällström, M., Koivisto, A.M., Janas, M. and Tammela, O. (2006) Laboratory Parameters Predictive of Developing Necrotizing Enterocolitis in Infants Born before 33 Weeks of Gestation. *Journal of Pediatric Surgery*, **41**, 792-798. https://doi.org/10.1016/j.jpedsurg.2005.12.034

[34] Muchantef, K., Epelman, M., Darge, K., Kirpalani, H., Laje, P. and Anupindi, S.A. (2013) Sonographic and Radiographic Imaging Features of the Neonate with Necrotizing Enterocolitis: Correlating Findings with Outcomes. *Pediatric*

Radiology, **43**, 1444-1452. https://doi.org/10.1007/s00247-013-2725-y

[35] Shah, D. and Sinn, J.K. (2012) Antibiotic Regimens for the Empirical Treatment of Newborn Infants with Necrotising Enterocolitis. *Cochrane Database of Systematic Reviews*, **8**, Article ID: CD007448. https://doi.org/10.1002/14651858.CD007448.pub2

[36] Solomkin, J.S., Mazuski, J.E., Bradley, J.S., *et al*. (2010) Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clinical Infectious Diseases*, **50**, 133-164. https://doi.org/10.1086/649554

[37] Moss, R.L., Dimmitt, R.A., Barnhart, D.C., *et al*. (2006) Laparotomy versus Peritoneal Drainage for Necrotizing Enterocolitis and Perforation. *New England Journal of Medicine*, **354**, 2225-2234. https://doi.org/10.1056/NEJMoa054605

[38] Phad, N., Trivedi, A., Todd, D. and Lakkundi, A. (2014) Intestinal Strictures Post-Necrotising Enterocolitis: Clinical Profile and Risk Factors. *Journal of Neonatal Surgery*, **3**, Article No. 44. https://doi.org/10.47338/jns.v3.134

[39] Martin, C.R., Dammann, O., Allred, E.N., *et al*. (2010) Neurodevelopment of Extremely Preterm Infants who had Necrotizing Enterocolitis with or without Late Bacteremia. *The Journal of Pediatrics*, **157**, 751-756. https://doi.org/10.1016/j.jpeds.2010.05.042

[40] Jiang, S.Y., Yan, W.L., Li, S.J., *et al*. (2020) Mortality and Morbidity in Infants <34 Weeks' Gestation in 25 NICUs in China: A Prospective Cohort Study. *Frontiers in Pediatrics*, **8**, Article 33. https://doi.org/10.3389/fped.2020.00033

[41] Eaton, S., Rees, C.M. and Hall, N.J. (2017) Current Research on the Epidemiology, Pathogenesis, and Management of Necrotizing Enterocolitis. *Neonatology*, **111**, 423-430. https://doi.org/10.1159/000458462

[42] Jones, I.H. and Hall, N.J. (2020) Contemporary Outcomes for Infants with Necrotizing Enterocolitis—A Systematic Review. *The Journal of Pediatrics*, **220**, 86-92. https://doi.org/10.1016/j.jpeds.2019.11.011

[43] Lucas, A. and Cole, T.J. (1990) Breast Milk and Neonatal Necrotizing Enterocolitis. *Lancet*, **336**, 1519-1523. https://doi.org/10.1016/0140-6736(90)93304-8

[44] Garg, B.D., Kabra, N.S. and Bansal, A. (2019) Role of Delayed Cord Clamping in Prevention of Necrotizing Enterocolitis in Preterm Neonates: A Systematic Review. *The Journal of Maternal-Fetal & Neonatal Medicine*, **32**, 164-172. https://doi.org/10.1080/14767058.2017.1370704

[45] Rabe, H., Gyte, G.M., Díaz-Rossello, J.L. and Duley, L. (2019) Effect of Timing of Umbilical Cord Clamping and Other Strategies to Influence Placental Transfusion at Preterm Birth on Maternal and Infant Outcomes. *Cochrane Database of Systematic Reviews*, **9**, Article ID: CD003248. https://doi.org/10.1002/14651858.CD003248.pub4

[46] Eidelman, A.I., *et al*. (2012) Breastfeeding and the Use of Human Milk. *Pediatrics*, **129**, e827-e841. https://doi.org/10.1542/peds.2011-3552

[47] Quigley, M. and McGuire, W. (2014) Formula versus Donor Breast Milk for Feeding Preterm or Low Birth Weight Infants. *Cochrane Database of Systematic Reviews*, **4**, Article ID: CD002971. https://doi.org/10.1002/14651858.CD002971.pub3

[48] 早产儿母乳强化剂使用专家共识工作组, 中华新生儿科杂志编辑委员会. 早产儿母乳强化剂使用专家共识[J]. 中华新生儿科杂志, 2019, 34(5): 321-328.

[49] 中国医师协会新生儿科医师分会循证专业委员会. 早产儿喂养不耐受临床诊疗指南(2020) [J]. 中国当代儿科杂志, 2020, 22(10): 1047-1055.

[50] Olsen, R., Greisen, G., Schroder, M. and Brok, J. (2016) Prophylactic Probiotics for Preterm Infants: A Systematic Review and Meta-Analysis of Observational Studies. *Neonatology*, **109**, 105-112. https://doi.org/10.1159/000441274

[51] FAO/WHO (2002) Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food. FAO/WHO, London.

[52] Deshpande, G., Rao, S. and Patole, S. (2015) Probiotics in Neonatal Intensive Care—Back to the Future. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, **55**, 210-217. https://doi.org/10.1111/ajo.12328

[53] Servin, A.L. (2004) Antagonistic Activities of Lactobacilli and Bifidobacteria against Microbial Pathogens. *FEMS Microbiology Reviews*, **28**, 405-440. https://doi.org/10.1016/j.femsre.2004.01.003

[54] Indrio, F., Riezzo, G., Raimondi, F., Biscegli, M., Cavallo, L. and Francavilla, R. (2009) Effects of Probiotic and Prebiotic on Gastrointestinal Motility in Newborns. *Journal of Physiology and Pharmacology*, **60**, 27-31.

[55] Indrio, F., Riezzo, G., Raimondi, F., Biscegli, M., Cavallo, L. and Francavilla, R. (2008) The Effects of Probiotics on Feeding Tolerance, Bowel Habits, and Gastrointestinal Motility in Preterm Newborns. *The Journal of Pediatrics*, **152**, 801-806. https://doi.org/10.1016/j.jpeds.2007.11.005

[56] Khailova, L., Dvorak, K., Arganbright, K.M., *et al*. (2009) Bifidobacterium Bifidum Improves Intestinal Integrity in a Rat Model of Necrotizing Enterocolitis. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **297**,

G940-G949. https://doi.org/10.1152/ajpgi.00141.2009

[57] Guo, S., Guo, Y., Ergun, A., Lu, L., Walker, W.A. and Ganguli, K. (2015) Secreted Metabolites of bifidobacterium infantis and Lactobacillus acidophilus Protect Immature Human Enterocytes from IL-1β-Induced Inflammation: A Transcription Profiling Analysis. *PLOS ONE*, **10**, e0124549. https://doi.org/10.1371/journal.pone.0124549

[58] Veckman, V., Miettinen, M., Pirhonen, J., Sirén, J., Matikainen, S. and Julkunen, I. (2004) *Streptococcus pyogenes* and *Lactobacillus rhamnosus* Differentially Induce Maturation and Production of Th1-Type Cytokines and Chemokines in Human Monocyte-Derived Dendritic Cells. *Journal of Leukocyte Biology*, **75**, 764-771. https://doi.org/10.1189/jlb.1003461

[59] de Waard, R., Garssen, J., Bokken, G.C. and Vos, J.G. (2002) Antagonistic Activity of *Lactobacillus casei* Strain Shirota against Gastrointestinal Listeria monocytogenes Infection in Rats. *International Journal of Food Microbiology*, **73**, 93-100. https://doi.org/10.1016/S0168-1605(01)00699-7

[60] Hori, T., Kiyoshima, J. and Yasui, H. (2003) Effect of an Oral Administration of Lactobacillus casei Strain Shirota on the Natural Killer Activity of Blood Mononuclear Cells in Aged Mice. *Bioscience*, *Biotechnology*, *and Biochemistry*, **67**, 420-422. https://doi.org/10.1271/bbb.67.420

[61] Kato, I., Tanaka, K. and Yokokura, T. (1999) Lactic Acid Bacterium Potently Induces the Production of Interleukin-12 and Interferon-γ by Mouse Splenocytes. *International Journal of Immunopharmacology*, **21**, 121-131. https://doi.org/10.1016/S0192-0561(98)00072-1

[62] Pammi, M. and Abrams, S.A. (2015) Oral Lactoferrin for the Prevention of Sepsis and Necrotizing Enterocolitis in Preterm Infants. *Cochrane Database of Systematic Reviews*, **2**, Article ID: CD007137. https://doi.org/10.1002/14651858.CD007137.pub4