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新生儿坏死性小肠结肠炎肠内营养策略

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摘　要

新生儿坏死性小肠结肠炎(neonatal necrotizing enterocolitis, NEC)常见于全球新生儿重症监护室(neonatal intensive care unit, NICU)，尤其多发生在那些早产或低出生体重的新生儿，该病以肠道继发坏死病变为特点，是一种新生儿毁灭性疾病，如不早期发现并及时干预，生存机会极低，即使存活临床医生也仍需面临与之相关的严重且复杂的后遗症问题，且该病还有一定的复发风险。虽然针对病因治疗该病还无从下手，但就目前众多NEC预防与治疗管理策略中可以知道合理的喂养指导可以降低NEC发生率，并安全尽快地为早产儿或NEC患儿建立足够的肠内营养支持。围绕NEC营养方面的知识仍存在很大差距，需要更多的研究来确定预防NEC或NEC后的最佳喂养方法，本综述旨在讨论营养和喂养方式在坏死性小肠结肠炎(NEC)中的作用，为NEC相关营养管理提供一些参考依据。

关键词

新生儿坏死性小肠结肠炎，肠内营养，喂养，营养

Enteral Nutrition Strategy for Neonatal Necrotizing Enterocolitis

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Abstract

Neonatal necrotizing enterocolitis (NEC) is common in neonatal intensive care unit (NICU), especially in premature or low birth weight neonates. NEC is characterized by intestinal necrotic lesions. It is a devastating neonatal disease. If it is not detected early and intervened in time, the survival chance is extremely low. Even if it survives, clinicians still have to face serious and complex sequelae related to it, and the disease still has a certain risk of recurrence. Although there is no way to treat the disease according to the etiology, we can know that reasonable feeding guidance can reduce the incidence of NEC and establish enough enteral nutrition support for premature infants or children with NEC safely and as soon as possible. There is still a big gap in the knowledge of NEC nutrition. More research is needed to determine the best feeding method for preventing NEC or after NEC. The purpose of this review is to discuss the role of nutrition and feeding methods in necrotizing enterocolitis (NEC) and provide some reference for NEC-related nutrition management.

Keywords

Neonatal Necrotizing Enterocolitis, Enteral Nutrition, Feeding, Nutrition

1. 背景

新生儿坏死性小肠结肠炎(neonatal necrotizing enterocolitis, NEC)具体的发病机制尚不清楚，可能与早产婴儿不成熟肠道局部微生物群结构组成失调[1] [2]和局部甚至全身炎性免疫反应有关。在大多数新生儿重症病房(NICU)中，早产儿或极低出生体重儿(very low birth weight infant, VLBWI)、超低出生体重儿(extremely low birth weight infant, ELBWI)与 NEC 患儿最初的营养来源主要靠肠外营养(parenteral nutrition, PN)维持，由于惧怕 NEC 的高死亡率[3]或 NEC 的复发，临床医生面临肠内营养启动延迟及推进缓慢的问题，长期的肠外营养导致感染与代谢并发症的风险增加[4] [5]，致使住院时间延长，对婴儿的生长发育造成严重影响。

2. 早期喂养与 NEC

2.1. 早期肠内营养

过去人们认为延迟进行肠内营养会降低早产儿 NEC 的发病率，但后来陆续的研究表明过长的禁食时间反而使肠道适应性改变，导致耐受性降低，肠上皮凋亡、肠粘膜萎缩、绒毛及隐窝数量减少[6] [7]，并且发现相比在早产儿出生 7 天后或者更长时间禁食后开始喂养，早期喂养(生后 96 小时内)一周内 NEC 的发生率并未增加[7]，所以现今研究者们更倾向接受进行早期肠内营养，当然它并不能预防 NEC 的发生。早期开始肠内营养对那些早产儿和或极低出生体重婴儿(very low birth weight infant, VLBWI)、超低出生体重儿(extremely low birth weight infant, ELBWI)似乎是比较安全有益的，Alshaikh 等学者曾做过一项荟萃分析，比较了不同肠内喂养量在开始早期肠内营养过程中的安全性，结果是 NEC 和喂养不耐受(feeding intolerance, FI)的发生率没有差异[8]。

2.2. 初始喂养量

就初始喂养量来说，目前国内外比较推荐早期微量喂养，早期微量喂养指的是对于 VLBW 婴儿可予以 10~20 ml/kg/d 的初始喂养量，加拿大诸学者发表的一篇关于极低出生体重儿喂养指南中谈到对于体重 < 1000 g 的 ELBWI 初始喂养量为 15~20 ml/kg/d，对于大于 1000 g 的可考虑 30 ml/kg/d [9]，还有研究发现初始喂养量超过 30 ml/kg/d 不会增加NEC的发生率反之还能缩短 VLBW 儿达到全肠内营养(total enteral nutrition, TEN)的时间[10]。目前对早期喂养量选择还尚具争议，可能更多的是需要对患儿制定一个针对自身情况的个体营养计划，总之适当的初始喂养奶量给了肠道适应的负荷，同时减少喂养期间喂养不耐受的发生[11]，为更早达到全肠内营养(TEN)创造基础条件。

3. NEC 后再喂养

3.1. 早期再喂养

在诊断 NEC 后，一般是建议禁食肠道休息 7~10 天，过长的禁食时间是可不取的，禁食后的早期再喂养与前面所述同样重要。Brotschi 等学者的一项的回顾性分析发现接受早期(<5~7 天)和晚期(>5 天或者 7 天)喂养，5 天内的患儿出现导管相关性败血症较少[12]，Wilson 等回顾性分析了从诊断 NEC 后早期再喂养(<7 天)和晚期再喂养(>7 天)的进食的结果，发现 NEC 后肠狭窄、NEC 复发甚至死亡等结果在早期与晚期再喂养组之间没有显著性差异[13]。另外有两项 meta 分析发现早期肠内营养似乎与包括 NEC 复发在内的一些不良后果无关，可见 NEC 后选择早期再喂养是明智的。

3.2. 初始喂养量

NEC 后重启喂养初始喂养量与前相同，暂没有明确定论。对于肠切除的 NEC 患儿术后初始肠内营养量目前国际上也无统一规定，Brotschi [12]等建议以 10 ml/kg/d 起始推注喂养。Shores [14]等人建议 20 ml/kg/d 推注喂养，对于 VLBWI 则以 15 ml/kg/d 起始推注喂养。Christian [15]等建议以 20 ml/kg/d 起始连续喂养。总的来说，大多数研究建议在 10~20 ml/kg/d，当然也有人采用更谨慎更少量的方法，但多数是针对那些 ELBW 的婴儿。

4. 喂养方式

4.1. 加奶速度

不管是对于早产或低出生体重的婴儿，亦或是诊断为 NEC 或 NEC 术后的患儿，关于喂养期间增加奶量的速度，目前还尚无统一定论，更多倾向于参考国外管理指南，推荐奶量增加速度为 15~35 ml/kg/d。Dorling 等人的一项大样本随机对照试验比较了缓慢加量(18 ml/kg/d)与快速加量(30 ml/kg/d)喂养下，极早产或极低出生体重婴儿在 24 月时没有中到重度神经功能障碍的存活率没有显著差异，且快速加量喂养也不会增加 NEC 的发生率[16]。另有一项临床试验比较了在出生小于 34 周，体重在 1000~1499 g 的早产儿中以 20 ml/kg/d 和 30 ml/kg/d 增量速度喂养的结局，结论是快速的肠内营养推进减少了达到全肠内营养的天数以及 PN 和静脉输注(IVF)的天数，而不会导致更大的喂养不耐受[17]。其它可参考的相关高质量研究有限，但是可以知道的是奶量增加的速度除受体重、饲料类型、全身情况等影响外，还部分取决于喂养期间患儿耐受情况，所以今后制定个体化喂养可能是有必要的。

4.2. 喂养形式

对于喂养的连续过程一般划分为持续性喂养与间歇性喂养，持续性喂养指的是持续 20~24 h 维持泵奶喂养，间歇性喂养指间隔 2~3 小时喂养一次[18]。最近的一项荟萃分析表明与间歇喂养相比，连续喂

养婴儿达到完全喂养的时间更长，其他变量无显着差异，如喂养不耐受、住院时间、恢复出生体重的天数、肠外喂养的持续时间、体重增长、身长增长、头围增长等，间歇性喂养可能对低出生体重婴儿更有益[19]。尽管如此仍需要更多的精心设计的研究和循证的临床实践来确定低出生体重早产儿最合适的喂养方法。目前国内一般采用可能更适应肠道生理的间歇性喂养，间隔时间也大多选择在 3 h，这可能与较长的进食间隔可以在两次进食之间允许更多的胃排空及为未成熟的消化道提供休息时间有关。最新的一项系统评价表明在稳定的早产儿(1000~1500 g)中，可以安全地遵循每三小时喂养一次。对于体重 < 1000 g 的婴儿，没有足够的证据建议最佳喂养间隔，但 2 小时的间隔可能更可取[20]。当然实际情况中还要根据喂养期间婴儿耐受情况、喂养并发症、家长意愿等来调整。

5. 营养形式

5.1. 配方奶及特殊类型奶

以牛奶为基础的配方奶是早产儿坏死性小肠结肠炎术后重启肠内喂养的一种选择，它能够提供生长所需的足够能量及营养元素[21]，并且临床上易于获得。但是一些研究表明配方奶可能会增加 NEC 的风险[22]，这可能与其内某些成分有关，致肠内菌群模式失衡从而促进炎症发生[23]。对于本已遭受过一次炎症或手术打击的患儿可能是不合适的，当然在没有合适替代乳制品的情况下可视临床情况使用。其它特殊类型的配方奶，例如深度水解蛋白配方奶、氨基酸奶等，它们属于要素型早产儿配方奶，是经过生物技术加工的不含整蛋白的短肽类或氨基酸类替代乳制品，它们可减轻肠道负担，利于肠道消化吸收[24]，相比早产儿配方奶，能够显著减少喂养不耐受的发生，能缩短达到全肠内营养时间[25]，国外一项研究发现要素配方奶可以提高肠细胞耐性，阻碍肠道促炎过程[26]，这对 NEC 患儿术后重启肠内营养十分有益。

5.2. 捐赠母乳

与早产儿配方奶及特殊类型配方奶相比，捐赠母乳(DHM)也是一种不错的喂养选择。相比配方奶，捐赠母乳具有保护性，其被证明能够降低 NEC 的发病风险，即便是配方喂养的早产儿或低出生体重婴儿有更快的体重增长[21] [27] [28]。DHM 与母乳一样具有良好的耐受性并含部分与之相同的有益成分，但由于其受消毒灭菌及保存时间等问题限制，其成分包括蛋白质含量、效价等会略低于母乳[29]，尽管如此，在有条件下捐赠乳仍可被推荐作为优质的营养替代乳品。

5.3. 母乳

母乳是新生儿最天然、最合适的营养要素[30]，它可以加快发育中的肠道趋于成熟以抵抗某些来自肠道的感染，降低全身感染风险[31] [32]，对于早产儿而言，其营养收益是巨大的。相比合成的配方奶，已有多项证据表明以母乳为主的喂养方式可降低新生儿坏死性小肠结肠炎(NEC)的发生率和死亡率[33] [34]，这很大可能需归咎于母乳能更优地增加婴儿肠道微生物群落的多样性以及更好的喂养耐受性，Steven 团队以一项前瞻性的研究指出了相比其它奶制品母乳更具优先级[35]。新生儿坏死性小肠结肠炎(NEC)越来越多得被认为与肠道微生物及免疫发育相关。肠道菌群失调引起的微生物群异常组成模式被认为是早产儿发生 NEC 的因素之一[36]，一项研究发现 NEC 患儿肠道中变形杆菌、大肠杆菌、肺炎克雷伯杆菌和葡萄球菌等比例有所增加，双歧杆菌、放线菌及拟杆菌数量减少[37]，虽然目前还不清楚这些菌群组成模式是如何致病的，但至少我们知道母乳可以显著提高肠道中双歧杆菌和拟杆菌等肠道有益菌的数量，从而改善肠道功能，增加肠道抵抗力，很大程度上使得预防早产儿发生 NEC 及其治疗显得不那么棘手。当然母乳中的有益成分也是重要的，就目前的研究来看，母乳中的一些防御成分被确定，包括人乳低聚糖、乳铁蛋白、sIgA、血小板活化因子乙酰水解酶以及一些生长因子[38] [39] [40]，如：转换生长因

子 β (TGFβ)、表皮生长因子(EGF)和促红细胞生成素(EPO)等[41]，这些被证实可增加婴儿肠道对外界不良事件的抗性，可抑制过度激活的肠道炎症反应及促进肠上皮生长修复等。有实验证据表明母乳可抑制Toll样受体(toll-like receptos, TLRs)中TLR4介导的信号传导[42]，通过影响notch信号通路，抑制肠上皮凋亡。尽管目前尚未明确母乳是如何预防NEC的具体机制，但可以确定母乳作为当前最主要的喂养手段无法被轻易替代，当然如果未来人工合成奶制品的优效性可与母乳媲美甚至优胜于其，未尝不是一场造福人类社会的时代性突破。

5.4. 强化母乳

母乳强化剂作为主要针对早产儿的一种强化营养，含有蛋白质、钙、磷、维生素、微量元素混合成分能够弥补早产儿母乳的不足，因有时纯母乳喂养不能满足低体重早产儿生长所需的蛋白质和矿物质等需要[43]，故在有条件时可为其提供母乳强化剂支持。Mukhopadhyay [44]等将166例VLBW儿随机分为母乳强化剂组和单纯母乳组，结果表明强化母乳组能达到更快的体质量增长，表现出更好的生长发育。国外已有大量数据表明母乳强化剂能很好地促进早产儿短期体重、身长、头围的增长，是公认的最佳营养选择之一。

6. 总结

NEC是早产儿最致命的肠道疾病，因其复杂的发病机制尚未阐明，使临床医生目前不得不放眼在预防及治疗上，然而尽早并安全地建立足量的肠内营养支持，可使那些风险患儿未成熟肠道逐渐适应外界环境，并更好地汲取营养获得足够的抵御疾病消耗的体质量，满足各器官系统的生长发育，缩短住院时长，减少住院期间并发症或术后并发症的发生率，所以安全合理地实施肠内营养管理是有必要的。

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