doi：10.7499/j.issn.1008-8830.2312089

综述

贫血与新生儿坏死性小肠结肠炎发病关系的研究进展

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［摘要］新生儿坏死性小肠结肠炎（necrotizing enterocolitis, NEC）是早产儿最常见的肠道炎症性疾病，具有较高的发病率及病死率。目前NEC的发病原因及机制尚不明确，多因素共同参与了NEC发生发展的过程。近年有研究发现，贫血是新生儿发生NEC的危险因素之一，但具体的发病机制尚不清楚。该文综述了近年来贫血与NEC发病关系的相关研究，为进一步认识贫血对肠损伤的影响及与NEC的关系提供参考。

［中国当代儿科杂志，2024，26（6）：646-651］

［关键词］贫血；坏死性小肠结肠炎；肠损伤；新生儿

Research progress on the relationship between anemia and neonatal necrotizing enterocolitis

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Abstract: Neonatal necrotizing enterocolitis (NEC) is the most common inflammatory intestinal disease in preterm infants, with a high incidence and mortality rate. The etiology and mechanisms of NEC are not yet fully understood, and multiple factors contribute to its occurrence and development. Recent studies have found that anemia is a risk factor for NEC in neonates, but the specific pathogenic mechanism remains unclear. This article reviews recent research on the relationship between anemia and NEC, providing a reference for further understanding the impact of anemia on intestinal injury and its association with NEC. **[Chinese Journal of Contemporary Pediatrics, 2024, 26(6): 646-651]**

Key words: Anemia; Necrotizing enterocolitis; Intestinal injury; Neonate

新生儿坏死性小肠结肠炎（necrotizing enterocolitis, NEC）是新生儿（尤其是早产儿）最常见和最具破坏性的炎症性肠道疾病，主要累及空肠和回肠。该病起病隐匿，临床表现以腹胀、呕吐、血便、腹泻等为主，病情进展迅速，严重者发生休克、肠穿孔及多器官功能衰竭[1]。NEC的发病率为2%~5%，以早产儿为主，早产儿发病率约为8%，极低出生体重儿的发病率为5%~16%；NEC的病死率为15%~30%，超早产儿（出生胎龄小于28周）的病死率约为40%，需手术治疗的早产儿病死率高达50%[2-4]。存活者可能遗留肠狭窄、短肠综合征、神经发育迟缓等严重并发症[5]，远期生存质量差。

NEC的发病机制尚不清楚，研究认为是多因素共同作用的结果，包括早产、喂养不当、肠道菌群失调、缺氧缺血、感染、输血等均是NEC的高危因素[6-8]。贫血是早产儿及极低出生体重儿常见的并发症之一，且随着出生胎龄及体重降低贫血程度越严重，出现时间也更早。贫血轻者可无任何症状，重者可能有呼吸暂停、喂养困难、继发感染、生长发育落后等表现。针对这类患儿，输血无疑是改善贫血症状、纠正贫血的一种有效

［收稿日期］2023-12-15；［接受日期］2024-04-16

［基金项目］2022年广东省基础与应用基础研究基金东莞市联合基金（粤莞联合基金）项目（2022A1515140063）；2023年东莞市社会科技发展（重点）项目（20231800935412）；2023年东莞市社会科技发展（重点）项目（20231800939962）。

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方法。然而，输血治疗并非没有风险，输血增加了NEC发生的风险，一部分患儿NEC发生在输血后48 h内[9]，因此有学者提出“输血相关性坏死性小肠结肠炎”的概念，但目前不能确定这种类型的NEC是红细胞输注所致还是受患儿自身贫血的影响，输注红细胞是否为NEC的独立危险因素仍存在较大争议。近年有研究发现，红细胞输注与NEC的发生无关[10-11]，相反，严重贫血是早产儿发生NEC的危险因素之一，且红细胞压积越低，NEC的发生风险越高[12-13]。一项多中心前瞻性队列研究显示，与没有严重贫血的婴儿相比，患有严重贫血的极低出生体重儿NEC的发生率显著增加[14]。Singh等[15]的研究表明，红细胞压积水平每下降1个百分点，极低出生体重儿NEC的发病风险就增加10%。目前，贫血相关NEC的作用机制尚不明确。本文针对贫血与NEC发病关系的相关研究进行综述。

1　贫血与肠道缺氧缺血

贫血是早产儿常见的并发症，早产儿生后因受促红细胞生成素产生不足、铁储备消耗、红细胞寿命短、骨髓造血低下、医源性失血等因素的影响使贫血情况更加复杂[16-17]。血红蛋白作为血液氧气的“搬运工”，对于器官组织供氧至关重要。贫血状态下血红蛋白的含量减少，导致运输氧气的能力下降及器官和组织的氧气供应减少。当血红蛋白含量太低无法满足器官组织的基本耗氧需求时，机体处于缺氧状态，各个器官和组织的功能都会受到影响，甚至导致细胞损害，则易造成机体损伤。

有研究表明，贫血可能导致内脏血氧饱和度降低及肠道组织缺氧，肠道氧合受损进一步导致亚临床肠道损伤，且这种肠道损伤随着血红蛋白水平降低越明显，这可能是诱发NEC的机制之一[18-19]。贫血引起血液携氧能力下降，导致组织氧合减少，使得肠道组织无氧代谢增强以及乳酸、酮体等代谢产物蓄积，同时这些无氧代谢副产物还会破坏肠道血管调节，引起肠道缺氧缺血性损伤[20]。组织缺氧时会导致有氧代谢产生的三磷酸腺苷（adenosine triphosphate, ATP）不足，细胞内ATP供不应求，需通过其他代谢途径来产生ATP以满足细胞内ATP的需求，其中包括糖酵解、肌酸激酶反应和腺苷酸激酶反应，但这些反应可引起细胞酸中毒、氧自由基形成、细胞内钙浓度增加及细胞膜磷脂被降解等变化进而导致细胞功能障碍甚至死亡[21]。Goldstein等[22]发现，在贫血期间由于肠道氧输送下降，无法满足新生儿喂养期间肠道因消化和吸收作用增加的需氧量，从而加重肠道组织缺氧性损伤。贫血引起的缺氧对肠道组织损伤和细胞能量代谢产生的不良影响可能启动NEC的发病。

同时，严重贫血状态下机体为了保证心、脑等重要脏器的氧供会启动血液重新分配机制，优先保障这些重要器官的血液供应，导致流向肠道的血流量减少，肠道氧合进一步下降，从而可能加剧肠道损伤[23]。此外，从胎儿期到新生儿早期过渡的阶段，胎儿休眠器官开始发挥消化和吸收营养物质的功能，肠道血管阻力会迅速发生改变，增加肠道血流量以适应新生儿开始通过肠道吸收营养物质的新状态。然而，贫血影响肠道血管阻力在过渡阶段的正常转变，使得肠道血流量减少，削弱早产儿肠内喂养的耐受性，造成缺血性肠损伤，甚至发展为NEC[24-25]。

这种因贫血引起的肠道黏膜缺氧缺血性损伤在红细胞输注后因氧化应激及再灌注损伤而加重，使贫血早产儿增加患NEC的风险，因此，维持临界红细胞压积及限制输血阈值的策略可能有助于降低NEC的发生率[26]。

2　贫血与肠道炎症损伤

过度的炎症反应是NEC发病过程中重要的环节，细胞因子及相关免疫细胞在NEC发生发展中发挥重要作用。大量炎症细胞聚集、浸润肠黏膜是NEC的一个关键病理特征，其中巨噬细胞是NEC发生发展过程中关键的免疫细胞[27-28]。巨噬细胞在NEC早期激活炎症信号并释放细胞因子形成促炎微环境，从而招募其他炎症细胞扩大炎症反应[29]。一项通过诱导贫血后输血引起新生小鼠NEC样肠损伤的动物研究显示，贫血和贫血后输血小鼠的肠道中均受到巨噬细胞浸润，这种巨噬细胞浸润是诱发输血相关NEC发生的重要因素[30]。在一项新生小鼠贫血模型的研究中发现，贫血本身导致的肠道缺氧通过上调缺氧诱导因子1（hypoxia inducible factor-1, HIF-1）而影响巨噬细胞功能，使巨噬细胞处于活化状态，活化的巨噬细胞分泌促炎细胞因子及抑制紧密连接蛋白ZO-1的

表达，增加肠道炎症和肠屏障通透性[31]。多项研究表明，NEC与炎症因子的增加有关，例如Toll样受体4（Toll-like receptor, TLR4）、核因子-κB（nuclear factor-kappa B, NF-κB）、肿瘤坏死因子（tumor necrosis factor, TNF）、干扰素-γ（interferon-γ, IFN-γ）、血小板活化因子、白细胞介素（interleukin, IL）-6、IL-8和IL-1β等，且炎症因子的水平与NEC的严重程度相关[32-34]。Arthur等[31]发现早产儿中血清INF-γ水平随着血红蛋白值的降低而增加，随后在贫血小鼠模型研究中表明，贫血可能通过增加肠道巨噬细胞的活性促进肠黏膜中促炎细胞因子INF-γ、TNF-α的产生。此外，缺氧情况下通过上调HIF-1增加巨噬细胞表面TLR4的表达，提高巨噬细胞对脂多糖的反应性[35-36]，激活TLR4介导的NF-κB通路，从而产生更多炎症介质，使肠道发生炎症反应的风险升高。由此推测，贫血引起的缺氧驱使TLR4/NF-κB信号通路的转导及进一步诱导大量促炎细胞因子的表达，增加了相关炎症因子的释放。研究表明，在NEC肠道组织中发现大量巨噬细胞，这种巨噬细胞与促炎巨噬细胞（M1型巨噬细胞）有着相似的表型，M1型巨噬细胞可产生促炎细胞因子导致炎症反应，有助于NEC的发生[37]。NEC的发生与过度炎症反应有关，其发生风险因缺氧、肠道菌群异常、缺血再灌注等因素引起的炎症触发介质而增加，然而贫血所诱发肠道炎症为触发炎症级联反应奠定了基础，从而增加NEC的易感性[38]。贫血使得肠黏膜处于轻微的炎症状态及肠道通透性增加，肠道对外界刺激的敏感性增加，在红细胞输注后会进一步加重激活巨噬细胞及分泌促炎细胞因子并抑制紧密连接蛋白的表达，增加肠屏障通透性，最终导致肠道损伤[39]。

3 贫血与肠道菌群失调

肠道菌群是驱动出生后免疫系统发育成熟和诱导免疫反应平衡的重要因素。肠道菌群失调在NEC的发展中起着重要作用，肠道致病菌和共生菌之间稳态的失调可破坏早产儿原本不成熟的肠道屏障，引发肠道炎症反应，进一步造成肠损伤从而导致NEC[40-42]。配方奶喂养、抗生素暴露和抑酸剂使用等因素可能通过影响肠道菌群增加NEC发生风险[43]。然而，一项研究证明，贫血可能是导致早产儿肠道菌群失调的潜在危险因素，而且肠道微生物的变化与贫血的严重程度相关[44]。该研究还发现随着红细胞压积越低，变形菌门的相对丰度增加，而厚壁菌门、拟杆菌门的丰度下降。这种以变形菌门占优势的肠道菌群失调与NEC患儿发病前的肠道菌群特征类似[45-46]。潜在的机制可能是贫血患儿本身存在储铁不足或者影响肠道铁吸收而引起机体缺铁，缺铁条件下可影响细菌代谢及短链脂肪酸的合成，导致肠道菌群多样性和优势菌丰度减少[47-48]。另一种潜在机制可能是贫血导致肠道缺氧，从而不利于肠道稳态的维持[49]。一项动物研究表明，缺氧可能通过促进小鼠肠道上皮细胞分泌血管生成素-4使梭状芽胞杆菌的丰度显著降低，而脱硫弧菌的丰度显著增加[50]。此外，该研究还发现脱硫弧菌所产生的磷脂代谢物促进IL-17A产生及γδ T细胞活化而诱发肠损伤。

研究显示，变形菌门细菌的脂多糖不仅会促进肠道炎症，还会削弱肠黏膜屏障功能，使得肠道黏膜更容易受到病原体的侵袭[51-53]。其次，变形菌的过度繁殖会抑制专性厌氧菌（双歧杆菌、梭菌等）的正常生长。这些厌氧菌能够合成丁酸、丙酸等短链脂肪酸，对肠道的健康至关重要。丁酸作为肠道上皮细胞的主要能量来源物质，不仅可促进肠道上皮细胞的成熟和增殖，还是抑制肠道促炎细胞因子释放的关键介质[54-55]，可抵御病原体侵入。因此，当变形菌过度繁殖而厌氧菌受抑制时，肠道内丁酸合成减少，不利于维持肠道上皮屏障的完整性以及限制肠道炎症反应的发生。贫血改变了肠道共生菌和致病菌共存的模式而引起肠道菌群失调，当致病菌过度生长时，肠道屏障功能被削弱，肠道炎症的风险随之增加，这种菌群失调和炎症之间的相互作用形成了恶性循环，加剧了肠道损伤，这也可能是贫血相关性NEC发生的潜在机制。

4 小结

综上所述，NEC的发生发展是多因素共同作用的结果，其中贫血是NEC的危险因素之一。目前贫血在NEC发病过程中的作用机制尚不明确。严重贫血引起肠道氧合受损及血流灌注减少，无氧代谢产物蓄积，对喂养耐受性差，易引起肠道缺氧缺血性损伤。同时贫血驱使巨噬细胞在肠道组织中浸润，促进促炎细胞因子释放，诱导肠道

炎症损伤。另外，贫血还可能引起肠道微生物失调，致病菌的繁殖进一步诱发并加重肠道炎症，破坏肠道黏膜屏障，导致NEC发生。目前仍有很多问题有待进一步研究，如肠道缺氧缺血性损伤所涉及的分子机制、炎症信号通路、贫血对黏膜屏障的影响等。因此，对于贫血在NEC中的作用机制还需要相关基础研究及临床研究进一步探索，从而制定更科学的贫血干预方案，以减少NEC的发生。

作者贡献声明：邓智月负责文献搜集及文章撰写；徐凤丹和何晓光对文章进行关键性修改；李宁审核及确定待发表文章的最终版本。

利益冲突声明：所有作者声明不存在利益冲突。

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（本文编辑：杨丹）