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炎症性肠病相关贫血的诊断与处理进展*

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摘要 贫血是炎症性肠病(IBD)常见且易被忽略的并发症,与IBD患者疾病转归和生活质量相关。IBD常见贫血类型为缺铁性贫血、慢性病性贫血和混合型。近年,IBD相关贫血的诊断和治疗均取得了进步。本文就IBD相关贫血诊断和治疗的进展作一综述。

关键词 炎症性肠病; 贫血; 诊断; 治疗

Advances in Diagnosis and Management of Anemia in Inflammatory Bowel Disease *LI Xueting, LI Jiajia, MAO Xiaqiong, LU Meijiao, LI Linzhen, ZHANG Hongjie. Department of Gastroenterology, the First Affiliated Hospital With Nanjing Medical University, Nanjing (210029)*

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Abstract Anemia is a common and easily being neglected complication of inflammatory bowel disease (IBD), and is related with disease prognosis and quality of life in IBD patients. The main types of anemia in IBD patients are iron deficiency anemia, anemia of chronic disease and mixed type. Nowadays, the diagnosis and treatment of IBD related anemia have made great progress. This article reviewed the progress in diagnosis and treatment of IBD related anemia.

Key words Inflammatory Bowel Disease; Anemia; Diagnosis; Therapy

炎症性肠病(inflammatory bowel disease, IBD)是一种慢性非特异性肠道炎症性疾病,包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD)。IBD患者常合并贫血。欧洲的研究显示,42%的IBD患者在诊断后第一年内出现贫血[1];IBD患者贫血的总体患病率约24%[2]。研究[3-4]发现,贫血IBD患者的生活质量较无贫血患者明显降低,持续性或复发性贫血与IBD患者存在侵袭性或致残性疾病有关。本文就IBD相关贫血的病因、类型、诊断和治疗等方面作一综述。

一、IBD相关贫血的病因和类型

IBD相关贫血的病因复杂,多种病因常合并存在。IBD患者因肠黏膜溃疡出血、饮食受限而发生铁缺乏。长期慢性炎症状态、铁调素表达上调可限制肠道铁的吸收,影响体内铁的分布。同时炎症因子水平上调使红细胞生成受抑、成熟障碍、寿命缩短;少数IBD患者因肠道手术、药物作用而出现维生素B_{12}、叶酸缺乏。此外,IBD治疗药物如硫嘌呤类药物可导致骨髓抑制[5];UC患者使用英夫利西单抗(infliximab, IFX)后出现自身免疫性溶血性贫血[6]。

IBD相关贫血的常见类型为缺铁性贫血(iron deficiency anemia, IDA)、慢性病性贫血(anemia of chronic disease, ACD)和混合型。此外,维生素B_{12}缺乏性贫血、叶酸缺乏性贫血、药物作用(如柳氮磺吡啶、5-氨基水杨酸、6-巯基嘌呤、硫唑嘌呤)导致的贫血也时有发生。

二、IBD相关贫血的诊断

根据世界卫生组织制定的贫血诊断标准,妊娠女性血红蛋白(hemoglobin, Hb)<110 g/L、非妊娠女性Hb<120 g/L和男性Hb<130 g/L诊断为贫血[7]。IDA和ACD是IBD相关贫血中较难区分的两种类型。2015年ECCO指南推荐,未合并炎症时(即缺乏生物学指标如CRP、ESR、白细胞计数或临床证据如腹泻、便血或内镜下表现等证实存在炎症),血清铁蛋白(serum ferritin, SF)<30 μg/L,或合并炎症时,血清SF<100 μg/L,考虑诊断为IDA。合并炎症时,SF>100 μg/L,转铁蛋白饱和度(transferrin saturation, TfS)<20%,考虑ACD;而SF为30~100 μg/L时,考虑混合型贫血[8]。但SF不仅受性别的影响,还是一种急性期蛋白,在疾病活动时,SF明显升高,可掩盖缺铁状态。

可溶性转铁蛋白受体(soluble transferrin receptor, sTfR)和可溶性转铁蛋白受体指数(sTfR/log ferritin index, sTfR-F)因不受炎症影响而被认为是两项有应用前景的指标[9-10]。sTfR作为膜结合转铁蛋白受体的一种蛋白水解酶衍生物,可反映机体铁状态。在缺铁状态下,sTfR水平升高;sTfR-F与CRP或疾病活动度无相关性[9]。sTfR-F<1表示仅存在ACD;sTfR-F>2表示ACD合并铁缺乏[10]。最近一项儿童IBD相关贫血的研究[11]发现,sTfR-F诊断ACD的准确性优于sTfR。然而,这两项指标检测费用昂贵,且缺乏统一的标

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准,故尚未大量应用于临床。

网织红细胞血红蛋白含量(reticulocyte hemoglobin content, CHr)是评估铁缺乏的有效指标。CHr≤30.3 pg 时,诊断 IBD 铁缺乏的敏感性为 82.2%,特异性为83.3%[12]。有研究[13]发现,CHr 对儿童 IBD 患者铁缺乏亦具有诊断价值。但 CHr 与 CRP 存在相关性,可能限制了 CHr 评估 IBD 患者铁缺乏的应用。

低色素红细胞百分比(percentage of hypochromic red cells, % Hypo-He)可显示 Hb 不足的成熟红细胞的比例,在 Hb 总体平均值变化之前增加。由于% Hypo-He 不受炎症影响,对判断 ACD 患者合并铁缺乏具有较好的可靠性。然而,目前尚缺乏研究评估% Hypo-He 诊断 IBD 患者合并铁缺乏的价值。

铁调素作为细胞铁输出的抑制剂,在铁稳态中起有关键的调节作用,可作为诊断 IBD 铁缺乏的指标之一。有研究发现, 铁调素≤2.0 nmol/L 可诊断 IDA,但铁调素受炎症的影响[14]。此外,铁调素的监测费用昂贵,可能限制了其在临床上的使用。

维生素 B_{12}或叶酸缺乏时,IBD 患者出现大细胞性贫血。血清维生素 B_{12}低于 200 pg/mL 且存在临床症状时,即可诊断维生素 B_{12}缺乏,当诊断不明确时,可参考同型半胱氨酸或丙二酸甲酯水平[15]。值得注意的是,若患者出现叶酸缺乏、原因不明的贫血或三系减少,应考虑有无药物的影响,必要时需更换治疗方案。

三、IBD 相关贫血的治疗

1. IDA 的治疗:铁缺乏是 IBD 相关贫血最常见的病因,一旦确诊,应立刻补充铁剂。IDA 的治疗目标为 4 周内将 Hb 水平提高至少 20 g/L 或提升至正常值,并补充铁储备,缓解贫血相关症状,从而改善生活质量。目前用于治疗 IBD 相关贫血的铁剂分为口服制剂和静脉制剂。补铁途径根据 IBD 患者的疾病活动度、并发症、贫血程度、经济状况等多个方面进行选择。

①口服补铁:口服补铁适用于病情处于缓解期、轻度贫血的 IBD 患者[16]。口服补铁方便,成本低,对青少年患者也有较好的疗效和耐受性[17]。临床常用的口服铁剂主要为亚铁制剂,如富马酸亚铁、硫酸亚铁、葡萄糖酸亚铁。新型口服铁剂麦芽酚铁可用于口服二价铁剂不耐受或无应答的 IBD 患者,可更快地恢复 Hb 水平,且对 IBD 疾病严重程度无明显影响[16,18]。有研究表明,口服铁剂的同时补充维生素 C 可促进铁剂的吸收[19]。维生素 C 一方面通过提供铁还原酶还原 Fe^{3+},增强铁的吸收,另一方面可减弱植酸盐和钙对铁吸收的抑制作用。一项研究[20]发现,补充维生素 D 有助于提高儿童 IBD 患者 Hb 水平。然而,口服补铁可能会引起消化道不良反应,增强肠道炎症。有研究[21]发现,口服铁剂会影响肠道细菌和粪便代谢产物。

②静脉补铁:静脉补铁适用于口服铁剂不耐受、Hb < 100 g/L、处于疾病活动期(CRP > 5 mg/L)或需红细胞生成刺激剂(erythropoiesis stimulating agents, ESAs)的患者。与口服补铁相比,IBD 患者使用静脉铁剂的耐受性更好,疗效更好[22-23],甚至可改善 IBD 患者的生活质量,减少住院频率,降低医疗费用[24-25]。目前常用于静脉注射的低分子量铁剂包括低分子右旋糖酐铁、蔗糖铁、葡萄糖酸铁,在使用过程中需少量多次给药,以避免不良反应如过敏、短暂性低血压等[26]。新型高分子铁剂羧麦芽糖铁可采用单次高剂量输注,已用于 IBD 患者贫血的治疗,具有良好的耐受性和疗效[27],且疗效优于口服铁剂、蔗糖铁等[28],对儿童和青少年 IBD 患者贫血亦有一定的疗效[29]。有研究[30]发现,IBD 患者使用 IFX 后单次高剂量使用羧麦芽糖铁,可有效治疗贫血,且费用降低。羧麦芽糖铁还可减少 IBD 贫血的复发[31]。此外,纳米氧化铁、异麦芽糖铁[32]正处于Ⅲ期临床研究中。

补铁的疗程因人而异,一般 Hb 恢复正常值后继续补充铁剂 4 ~ 6 个月。纠正铁缺乏的第一年内应每 3 个月监测铁含量,以后每 6 ~ 12 个月监测一次[8]。一旦患者再次出现 SF < 100 μg/L,或 Hb 低于正常值时应立即补铁[8]。缺铁的复发与铁储存有关,治疗后 SF > 400 μg/L 能预防未来 1 ~ 5 年内缺铁的发生,因此补铁的目标为 SF 含量超过 400 μg/L[33]。

③ESAs:IBD 相关贫血患者对静脉补铁治疗效果不佳时,可予 ESAs。ESAs 包括重组人红细胞生成素(recombinant human erythropoietin, rHuEPO)、达依泊汀-α 等,后者的半衰期更长,可延长用药间隔。有研究[34]证实,患者补铁治疗的同时联合 rHuEPO 治疗,可迅速升高 Hb。Koutroubakis 等[35]的研究发现,达依泊汀-α 联合静脉补铁有助于提高 IBD 贫血患者 Hb 水平。

2. ACD 的治疗:长期炎症状态是 IBD 患者发生 ACD 的主要病理生理机制,故控制炎症是治疗 ACD 的重要手段。靶向生物制剂已成为治疗 IBD 的重要药物,可明显改善血液学指标[36]。抗 TNF-α 可增加促红细胞生成素的生成和红细胞基因的表达,同时诱导黏膜愈合,减少失血和促炎因子的产生,从而抑制铁调素的产生[37]。目前,一些针对铁调素的新药物正在研发中,如铁调素抑制剂、铁调素抗体和干扰膜铁转运蛋白-铁调素相互作用制剂[38]。

3. 维生素 B_{12}和叶酸缺乏性贫血的治疗:对于有症状的维生素 B_{12}缺乏患者,推荐肌内或皮下注射维生素 B_{12}[39]。有数据表明经舌下和鼻管的给药方式有望成为维生素 B_{12}的给药方式[40]。若患者回肠切除 > 20 cm 需终生补充维生素 B_{12}[41]。对于叶酸缺乏的 IBD 患者,推荐口服补充叶酸[39]。值得注意的是,叶酸的摄取可能会掩盖维生素 B_{12}的缺乏,因此在补充叶酸前,需评估是否存在维生素 B_{12}缺乏。

四、IBD 相关贫血的监测

IBD 相关贫血在补铁后经常复发,尤其是在疾病活动度未能得到控制时[31],因此需行周期性检测。ECCO 指南建议,临床缓解期 IBD 患者应至少每 6 ~ 12 个月行 1 次贫血筛查,而活动期 IBD 患者应每 3 个月或更短时间内完善贫血相关检查;如 IBD 患者存在大细胞性贫血,应至少每年检测一

次维生素 B_{12} 和叶酸。全血细胞计数、SF、CRP 为 IBD 相关贫血的基本筛查内容[8]。

五、结语

总之,IBD 合并贫血常见,以 IDA、ACD 和混合型多见。新型生物学指标可提高 IBD 相关贫血的诊断准确性,新型铁剂可有效改善 IBD 患者贫血的缺铁状态,减少复发。IBD 相关贫血易被临床医师忽略,应提高对其的重视,有利于 IBD 患者的恢复。

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