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幽门螺杆菌感染与儿童营养不良的关系

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摘 要

幽门螺旋杆菌是一种多鞭毛、S状革兰阴性微需氧菌，感染产生免疫炎性反应，可能与儿童厌食、贫血、肠道疾病、生长发育迟缓及微量营养素缺乏有关。该文基于近年研究成果，针对儿童幽门螺旋杆菌感染营养不良问题进行综述，为儿童营养不良的诊疗提供一定思路。

关键词

幽门螺旋杆菌，感染，营养不良

Relationship between *Helicobacter pylori* Infection and Malnutrition in Children

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Abstract

***Helicobacter pylori* is a flagellum, sigmoid gram-negative aerobic bacterium, can produce immune inflammatory reaction, infection may be related to children anorexia, anemia, intestinal disease, growth retardation and micronutrient deficiencies. In this paper, based on the research results in recent years, the problem of malnutrition in children with *Helicobacter pylori* infection was reviewed, and some trains of thought for the diagnosis and treatment of malnutrition in children were provided.**

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Keywords

***Helicobacter pylori*, Infection, Malnutrition**

1. 引言

幽门螺旋杆菌(*Helicobacter pylori*, Hp)是一种多鞭毛、S 状革兰阴性微需氧菌，生存于胃十二指肠黏膜[1]。Hp 是最常见感染源之一，人口感染近一半以上，主要发生在儿童期[2]，感染率约为 33.3%，并每年呈下降趋势[3]。Hp 感染(HpI)主要以“口－口、粪－口”传播，人是重要传染源，有明显家族聚集现象，无疑增加了儿童感染的风险[4]。Hp 为 I 类致癌因子，产生毒力因子，使胃粘膜损失，更有甚者发生恶变[5]。Hp 具有广泛致病性，儿童感染与慢性胃炎、慢性腹泻和口腔疾病等密切相关，亦与许多消化道外疾病，如生长发育迟缓、缺铁性贫血(Iron deficiency anemia, IDA)、免疫性血小板减少症(Immune thrombocytopenic, ITP)、过敏性紫癜(Henoch-Schonlein purpura, HSP)、维生素 D 缺乏症(Vitamin D deficiency)有关[6]。儿童正处于生长发育关键阶段，免疫力及营养吸收较弱，疾病易感性增加，易出现营养不良。本文基于最近研究成果，针对儿童营养问题，对 Hp 感染相关疾病作以论述。

2. Hp 与慢性胃炎

儿童 Hp 感染消化道症状多无特异性，<3 岁儿童可有挑食、食欲不振症状，大龄组临床表现为恶心、呕吐、反酸、口臭、腹痛等反应，胃部症状较轻，多表现为慢性浅表性胃炎(chronic superficial gastritis, CSG) [7]，经证实，儿童慢性胃炎 Hp 感染率达 60%以上，根除 Hp 可使上述症状明显减轻[8]。一项国内病例对照研究中[9]，慢性胃炎 Hp 阳性患儿血清 CagA 抗体、VacA 抗体检测结果为 52.32%、6.97%，总体感染率达 59.30%，另一项回归分析表明，Hp 感染是 CSG 的影响因素($P < 0.05$)，对病例组患儿分析发现，各营养指标均低于对照组，说明 CSG 影响患儿营养状况，不利于儿童生长发育[10]；国外一项基于社区的横断面研究发现[11]，在有消化不良和 Hp 感染的患儿中，甚有抑郁症倾向，学龄期儿童社会心理压力较大，常伴精神负性因素，出现胃肠激素分泌紊乱，增加 CSG 发病风险。研究证实，Hp I 型感染易诱发胃粘膜萎缩，引起肠上皮化生及不典型增生[12]，CagA 可介导 Th1/Th2、Th17/Treg 等免疫反应失衡，产生多种促炎因子，如白细胞介素-1β (interleukin-1β, IL-1β)、白细胞介素-17 (interleukin-17, IL-17)及缺氧诱导因子-1α (hypoxia inducible factor-1α, HIF-1α)，与 HP 中性粒细胞活化蛋白(HP-NAP)协同促进单核细胞大量聚集，提高反应性氧化及蛋白水解[13]，Hp 毒力因子削弱胃黏膜屏障，诱导腺体分泌功能衰退，微量营养素吸收障碍[14]；VacA 通过 H^+-K^+-三磷酸腺苷(Adenosine triphosphate, ATP)酶使泌酸功能紊乱，影响细胞增生，导致空泡变性，还能干扰生长因子调节过程[15]。

3. Hp 与厌食

Hp 感染起初症状不明显，随着病情加重出现胃肠功能失调，引起消化道症状。Hp 感染可能与口腔疾病、功能性消化不良(Functional dyspepsia, FD) [16]等存在潜在关联，Hp 感染伴发牙周炎、口腔黏膜病可有口臭症状[17]。Hp 为机会致病菌，当机体免疫力低下时可由上消化道蔓延，滋生其他致病菌，影响进食；FD 患者胃泌素水平增高，胃酸分泌增加，可能导致反酸、食欲减退等症状，并发厌食症而引起消

瘦风险[18]，Hp 感染 FD 中嗜酸性细胞异常可破坏胃肠道屏障，影响胃肠神经功能，造成内脏敏感性升高与动力障碍[19]，还可能引起胃食管反流，加重炎症消耗，使食物热卡摄入不足，增加营养代谢，从而导致消瘦。

胃肠肌饿素(Ghrelin)属诱食肽类，对动物的采食作用与一些神经肽 Y(NPY)如增食因子(Orexin)有关[20]。现已发现 Ghrelin 通过生长激素促释放激素受体(GHS-R)，刺激下丘脑食欲中枢神经肽 YNPY/AGRP[21]，又正反馈生长激素(GH)促进胃肠动力，加快胃排空，亦直接调节胃肠功能促进食欲[22]。Hp 感染可影响 Ghrelin 分泌，Martín-Núñez GM 等[24]证实 Hp 感染者 Ghrelin 水平明显低于阴性者，Gennari L 等[25]在 CagA 阳性 HP 感染中也观察到 Ghrelin 水平降低，而 Ghrelin 分泌取决于感染时长、炎症程度等因素。蒋丽蓉等[25]研究显示 Hp 感染厌食患儿 Ghrelin-mRNA 表达水平较低，抗 Hp 治疗后有所上升，食欲及体质量增长，同时，刘捷[26]在对 171 名 Hp 感染患儿的研究中得到了与上述学者一致的结果；一项国外回顾性分析发现[27]，Hp 根除治疗后胃蛋白酶原 I/II 比率显着增加，组织学肠化生评分严重程度与总 Ghrelin 水平呈负相关，一项动物实验[28]发现 HpVacA 通过下丘脑尿皮质素 1 (Hypothalamic Urocortin 1)在小鼠中引起厌食和焦虑，食欲和体质量均明显下降，提示 Hp 感染厌食中还存在功能性因素，可能机制包括：a Hp 感染引起免疫反应，释放炎症因子，破坏 Ghrelin 细胞，导致分泌减少，通过外周性调节能量平衡[29]；b Hp 毒力 CagA、VacA 抗体，尤其是 s1/m1 基因型，调节 Hp 脂多糖(lipopolys-acchardes, LPS)诱导的胃黏膜炎症反应，干扰下丘脑体质量稳态脑区，致神经肽失衡[30]，生长素量下降，瘦素(Leptin, LP)、酪酪肽(peptide yy, PYY)水平升高，引起食欲下降。

目前，关于 Hp 感染与厌食相关性报道鲜少，发病机制的阐述也较模糊，但儿童 Hp 感染营养问题日益严重，相关问题有待进一步研究。

4. Hp 与发育迟缓

4.1. Hp 感染与生长迟缓(Growth Retardation, GR)

儿童感染 Hp 以 Th1、Treg 为主的免疫反应表现水平较轻，却有利于 Hp 定植于胃上皮内层，形成长久的炎症刺激[31]，造成营养状态低下，进而影响患儿生长发育。Meta 分析显示，Hp 感染与线性生长(OR = 1.76, 95% CI: 1.15~2.69, P = 0.01)有显著负关联，Hp 感染对年龄体长 Z(HAZ)评分有不利影响(SMD = −0.41, 95% CI: −0.69, −0.13; P < 0.01)，Hp 感染在消化道外主要表现为生长参数异常[32]。Wei S 等[33]观察发现，在 Hp 患病率 < 30%或 30%~50%的研究中，儿童生长延迟率更高(OR = 1.51, 95% CI: 1.28, 1.78)，尤其是线性生长(33.11%)。朱丹荣等[34]对 14 岁儿童 Hp 感染现状及生长发育分析，结果显示 Hp 阳性者身高、体质量及胸围更低；何昀等[35]对学龄期儿童 Hp 检测和生长发育研究表明，Hp 感染儿童 WHZ < −1、HAZ < −1 发生率远高于阴性者；王冰君等[36]对 90 例患儿 Hp 感染分型及营养状况评价发现，生长发育迟缓率达 27%，明显高于 Hp 阴性者。上述研究显示 Hp 感染与生长发育受限关系密切，可能原因为：

a) 炎性因子干扰下丘脑－生长激素－胰岛素样生长因子 1 (GH-IGF-1)轴，影响生长发育。除下丘脑因素外，适当胃泌素-17 (gsatrin-17, G17)可能参与 GH 的分泌，G17 和甲状腺激素轴(TSH-FT4/FT3)之间在生长和代谢过程中也存在联系，FT3 对 IGF-1 产生允许作用，反之，GH 在 IGF-1 介导的反应中，增强 FT4 到 FT3 单碘化最重要的激素之一是 G17，它既通过下丘脑间接调节上述激素的释放，又通过体细胞直接刺激 GH 的分泌[37]。据推测，Hp 感染会减少 G17 免疫阳性细胞的数量，抑制 G-17mRNA 的表达。研究证[38]，特发性身材矮小(ISS)伴 Hp 更瘦矮，乳糖吸收不良(LM)和胃肠道疾病(GIDs)发生率高，IGF-1 峰值、体质指数(BMI)较低，可能与 G17 分泌量少有关，或与分子模拟现象中相同的神经肽发生交叉反应，使 IGF-1 浓度降低，根除 Hp 后 G17、IGF-1 浓度及生长速度得到改善。Hp 感染可能导致 G17 分泌不足，并进一步调控 GH-IGF-1 和儿童生长速度[39]。

b) Hp 感染导致 FD，营养吸收不足，降低胃肠道黏膜屏障防御功能，黏膜损伤，胃酸分泌减少，渗透性增加，易导致腹泻[40]，营养素丢失过多，出现营养不良。Feng J 等[41]发现 Hp 感染是引起小儿肠炎的常见因素之一，在 Hp 引起 GIDs 中发现了微核糖核酸(miRNAs)异常表达，可能通过上调 IL-6、TNF-α 水平，诱导相关蛋白 Yap-1 及 miR-32-5p 增加，使肠上皮活力下降，相反，基于 Hp 感染对炎症性肠病(IBD)的潜在保护作用[42]，对于腹泻型 IBD，应谨慎 Hp 根治，特别是儿童。Hp 可与肠道菌群共生，与一些机会致病菌、厌氧菌呈负相关，对于长期无症状者，根除 Hp 可能影响微生物群丰度，胃肠菌群失调，加之抗生素及质子泵抑制剂(PPI)作用，导致消化道黏膜反应，微生物代谢途径、胃酸变化，微环境破坏，出现抗生素相关性腹泻(PPD) [43]，故对 Hp 的根除，应详尽评估，有必要加用益生菌[44]。

c) 社会经济卫生评分始终是微生物结构变化的最强预测因子，可能与肠道免疫环境变化有关，Hp 感染成为儿童健康的独立决定因素，影响生长发育[45]。

d) Hp 感染后代谢异常，加速能量消耗，机体出现病理生理改变。研究发现[46]，Hp 阳性患儿粪便中戊酸、丙酸、异丁酸等均增高，代谢综合征(MS)检出率也高于阴性者，Hp I 型尤为明显；Hp 感染与低血清白蛋白(albumin, ALB)、高球蛋白(globulin, GLO)水平和低白球比(A/G)显着相关，是影响营养代谢的重要因素[46]。国内学者[47]基于 HNMRD 代谢组学方法来探索 Hp 感染对儿童营养的影响，发现能量、氨基酸、脂质和微生物群代谢紊乱可能发挥重要作用。研究表明[48]，Hp 感染可增高氧化应激水平，减弱血清总抗氧化能力，可能是胰岛素抵抗指数(HOMA-IR)的独立预测因子。胰岛素抵抗(IR)是 MS 主要致病因素，Hp 与 IR 之间可能存在关联[49]。Meta 分析显示[50]，II 型糖尿病(T2DM)患者 Hp 根除失败较高，Hp 根除后糖化血红蛋白(HbA1c)得到改善(WMD = −0.33, 95% CI: −0.65, −0.02)，Bazmamoun H [51]研究指出，病程较长的 I 型糖尿病(T1DM)患儿，有感染 Hp 的风险，而 Esmaeili Dooki MR 等[52]研究发现，儿童 Hp 感染与 I 型糖尿病 T1DM 无显著相关性，合并和未感染 Hp 的 TIDM 血糖控制状况无差异，Bayrak NA [53]也得出了类似结果。T1DM 发病机制主要为胰岛素不足(ID)，T2DM 与 IR 相关，儿童在临床上有争议结果，建议进一步研究。

Hp 感染可能是儿童发育迟缓的潜在危险因素，两者之间机制尚待进一步明确。血清 IgG 法之间没有异质性，更客观反应持续感染，通过 IgG 对儿童生长障碍进行最佳评估[54]，Gonciarz W 等[55]发现应用衰减 Total 反射率傅里叶变换红外光谱法(FTIR)和人工神经网络可能有助于确认 Hp 导致的儿童生长异常，但相关指标并无特异性，加之环境因素、个体差异，有必要为生长迟缓建立一个统一标准定义。

4.2. Hp 感染与肥胖

双重营养不良负担(double burden of malnutrition, DNM)，即营养不足与超重肥胖并存[56]，肥胖作为营养不良问题，对儿童生长发育及社会经济有不利影响。肥胖与 Hp 感染之间的关系存在争议，肥胖可以改变先天性和适应性免疫，肥胖程度与免疫力下降之间存在关联。病态肥胖受试者单核细胞向巨噬细胞的成熟度较低，多形核杀菌能力降低。与同类别正常个体相比，严重肥胖患者 NK 细胞活性显着降低[57]。据推测[58]，氧化 NDA 损伤与 Hp 感染有关，在肥胖的脂肪细胞中，活性氧自由基(ROS)抑制胰岛素信号通路，激活内质网氧化应激及 NF-KB 信号通路，引发脂质过氧化、DNA 损伤和蛋白质修饰。Hp 感染 BMI 分位数与 8-羟基脱氧鸟嘌呤(8-OHdG，氧化应激生物标志物)水平线性相关，肥胖个体(BMI ≥ 30 kg/m^2) Hp 患病率高于偏瘦者(BMI < 25 kg/m^2) [59]，一项国外 Meta [60]示 Hp 感染风险与肥胖发生正相关，Hp 阳性者更容易肥胖，而 Pundak OY 等[61]在对 292 儿童研究发现，Hp 阳性儿童中超重 11.6%，肥胖 7.5% (29/146, 23/146)，Hp 阴性儿童中超重 10.3%，肥胖 8.9% (23/146, 30/146)，两组无差异，Hp 与儿童超重/肥胖之间并无关联，Hp 感染 CagA 抗体与 BMI 或血清 Leptin 水平无关；Moran-Lev H 等[62]前瞻性研究发现，有症状儿童中 Hp 定植与超重/肥胖存在负相关，Hanh D 等[63]在一项北美队列中表明 Hp 感

染可降低儿童肥胖患病率。肥胖主要取决于遗传代谢、生活习性、个体差异，相对于成人，Hp 对儿童肥胖的发生影响甚微，未来可探求相关性证据，完善儿童肥胖的发生机制。

5. Hp 与 IDA

5.1. 铁(Iron)的作用

铁为人体必需微量元素，可提高机体免疫力，增加中性粒细胞和吞噬细胞功能，亦能直接参与人体能量代谢。缺铁与贫血、厌食、神经功能障碍有关，影响儿童生长发育和认知活动[64]。

5.2. Hp 感染与铁

近年来，大量证据表明 Hp 与铁缺乏(iron deficiency, ID)之间存在一定关系。不明原因缺铁性贫血(iron deficiency anemia, IDA)中 50%以上是由 Hp 感染所致，根除 Hp 同时补充铁剂可改善铁状态标志物(铁蛋白 SF、Hb、平均红细胞体积 MCV、血清转铁受体水平 sTfR) [65]，Tanous 等[66]在有非缺铁性贫血(NAID)或 IDA 的患儿中，比较成功根除 Hp (无需补铁)之前和 6~9 个月后的 Hb、SF 和 CRP 水平，发现成功根除有助于改善难治性 NAID 或 IDA，年龄较大是 Hp 根除后贫血消退相关的唯一危险因素。早至 2015 年相关共识[67]已将不明原因 IDA 列为 Hp 根除的指征。Elsaadany E 等[68]探究儿童 Hp 感染与 SF 水平及治疗中发现，Hp 患儿 SF、Hb 水平显著降低，组织病理学异常严重程度与 SF、Hb 水平负相关，但与 sTfR 浓度正相关，根除 Hp 后上述指标恢复正常。从霞等[69]对 6~14 岁儿童 Hp 感染营养状况分析发现，感染组血清铁(SI)、SF、Hb 均明显低于非感染组($P < 0.05$)，Lupu A 等[70]回顾性研究 Hp 与贫血的相关性，显示 542 例感染 Hp 患儿中，48 例伴有小细胞低色素性贫血，其中 7 例(14.5%)伴缺铁，Hp 感染与儿童 ID 及 IDA 显着相关。然而，有学者[71]在单变量和多元逻辑回归分析中未发现 ID/IDA 与 Hp 感染之间存在关联，无论 Hp 治疗状态如何，大多数受试者的 IDA 都得到治愈；Zhang Y 等[72]发现 Hp 组 ID/IDA 发生率高于对照组($z = 9.112/9.112$, $P < 0.05$)，Hp 组 SI、SF、Hb 低于对照组，总铁结合力(TIBC)水平高于对照组($t = 7.630$, $P < 0.05$)，而 Hp 组平均红细胞血红蛋白浓度(MCHC)、红细胞分布宽度(RDW)与对照组比较无统计学意义，逻辑回归显示 Hp 感染不是 ID 的综合危险因素，可能与纳入者对 ID/IDA 的易感性低，或依存性较差、Hp 检出率有关。

5.3. IDA 发生机制

Hp 感染一定程度上影响铁代谢指标异常，干扰机体新陈代谢，引起 IDA 可能相关的因素为：

a) Hp 可增强一氧化碳合成酶(iNOS)活性，降低 Hb 合成，减弱造血功能[73]，通过铁抑制外膜蛋白(IROMP)，摄取宿主血红素[74]；Hp 感染后杀菌素含量下降[75]，铁元素在贮存、转运等方面受到影响。

b) Hp 感染引起胃十二指肠黏膜糜烂、溃疡，出现显隐性出血，导致 IDA 发生，加之上皮细胞渗透性增高，铁及 SF 迅速流失[76]。

c) Hp 可降低胃酸及维生素 C 水平，阻碍铁元素游离化，pH 升高又使坏血酸稳定性变化，生物利用度降低，减少二价铁吸收，同时高价铁通过 Fenton 反应产生自由基，损伤胃肠黏膜上皮[77]，铁吸收含量降低。

d) Hp 可表达与一种大小 19-kDaSF 类似 SF 的铁结合蛋白(Pfr)、乳铁蛋白结合蛋白(HLf)、非血红素含铁蛋白[78]，通过竞争性抑制铁的结合，反而促进自身增殖，造成恶性循环。此外，Hp 还表达亚铁高亲和力转运体、铁摄取调节因子(Fur) [79]，致铁稳态失衡，干扰铁的利用度。

e) Hp 感染释放 IL-1β、IL-6，刺激肝脏生成铁调素(hepcidin) [80]，负性调控铁代谢，还使巨噬细胞铁释放减少下调 SI [81]。

f) Hp 具有铁调节基因多态性，包括 CagA、vacA、fecA1、feoB、fdxA 在内的几种宿主相互作用基因[82]，尤其与高表达的唾液酸结合粘附素(sabA)在 IDA 发生中起协同作用[83]。

6. Hp 与维生素 D

脂溶性维生素 D 主要有维生素 D2 和维生素 D3 两种形式，经肝转化为活性维生素 D(VD)，如骨化三醇 1,25(OH)2D3，在钙稳态、免疫调节和细胞增殖中发挥重要作用[84]。经证实，VD 与 Hp 感染具有关联，一项 meta 分析[85]表明，Hp 感染会降低 VD 血清水平，根除 Hp 可逆转其不良反应，在一项纳入 312 例患者的横断面研究中发现 Hp 感染者 VD 水平较低，且与 Hp 根除率呈正相关[86]；Gao T 等[87]对婴幼儿研究显示，Hp 感染与 VD 缺乏症显着相关，此外，VD 水平 ＜10 ng/mL 可能增加 Hp 感染风险[88]。维生素 D 受体(VDR)抑制转录因子下调 IL-2 和 INF-γ 水平，Hp 感染时 VDR 表达上调，VDR 可维持胃黏膜稳态和抑制 Hp 炎症反应[89]。最近研究发现，IL-1β 和 TLR (Toll 样受体)激活时 VD 上调 β-防御素[90]，VD/VDR 复合物进一步与 CAMP (导管素抗菌肽)启动子结合以增加其表达，同时 VD3 可激活 PDIA3 (蛋白质二硫异构酶亚型 A3)受体，促使 Hp 通过自噬溶酶体降解[91]；1,25D3 通过 VDR 依赖性 c-Raf/MEK/ERK 途径保护胃粘膜上皮细胞免受 Hp 细胞凋亡[92]。因此，维生素 D 与 Hp 相互作用，VD 可减少氧化应激并进一步清除 Hp，未来可尝试联合 VD 对 Hp 进行根治，但需进一步评估验证。

7. Hp 与锌

锌(znic, Zn)稳态主要依赖于肠道吸收，可维持膜屏障并调节免疫反应，粒细胞趋化、NK 细胞活性和 ROS 的产生取决于 Zn 浓度，Zn 水平不足会影响生长发育、神经感觉和内分泌活动。Zn 可诱导 Hp 产生炎症，如 CagA 易位、NF-κB 及 IL-8 表达[93]，Hp 毒力因子钙卫蛋白(S100A8/A9 异二聚体)、钙粒蛋白 C (S100A12 同二聚体)在内的宿主抗菌蛋白通过 CadA、CrdB-CzcAB 复合体和 CznABC 三种 Zn 转运系统获取锌元素[94]。一项基于 RNA 测序的 Zn 调节反应研究表明，高浓度的 Zn 与 Hp 核糖体亚基、分子伴侣和粘附素相关的基因上调有关，然而，鞭毛组装基因和一些 IV 型分泌系统基因被抑制，在应激条件下 Zn 具抗菌活性[95]。Bernegger S 等[96]利用一种新型荧光共振能量转移(FRET)肽揭示了 Zn 和 Cu 结合可抑制 Hp 丝氨酸蛋白酶 A(HtrA)高温需求，有助于抗 Hp 感染；Duzgun Ergun D 等[97]发现，在 Hp 阳性慢性胃炎患者中血清 Zn 水平降低，Cu/Zn 比值升高，Hp 影响患者微量元素代谢；赵张颖的研究[98]也发现 Hp 感染与 Zn 缺乏有关，对 Hp 感染患儿必要时补 Zn，以减少对生长发育的影响[99]。由于 Zn 在 Hp 和宿主免疫系统中作用复杂，需进一步研究 Zn 生物利用度与 Hp 炎症之间的关系。

8. 结语

Hp 感染与儿童营养代谢之间关系密切，疾病谱也较广泛，而致病机制尚不明确。Hp 分型对各指标影响较大，在临床方面的应用并不广泛，Hp 多重耐药性不断增加，缺乏精准诊疗，加之呼吸道病原(如 COVID-19、H1N1)影响，易忽视儿童 Hp 营养代谢问题，未来有必要进行营养不良干预性研究，研制疫苗及新型抗菌素，对 Hp 积极根治及营养支持，改善儿童身心健康。

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