

## 胃食管反流病的个体化诊疗

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### Individualized medicine of gastroesophageal reflux disease

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### Abstract

Gastroesophageal reflux disease (GERD) is a common disease worldwide, and its prevalence is increasing in both developed and developing countries. GERD is divided into three subtypes, namely, erosive esophagitis, nonerosive reflux disease (NERD), and Barrett's esophagus. The etiology, pathogenesis, clinical manifestations, and response to treatment of GERD invariably show high heterogeneity or significant individual difference, especially NERD and refractory GERD. On the other hand, advanced technology has currently provided a wide range of methods for the diagnosis and treatment of GERD patients; however, the long-term efficacy and quality of life of some patients are unsatisfactory. Therefore, each GERD patient needs a specialized management strategy aiming at his/her own condition, which is known as individualized medicine or personalized medicine. The goal of GERD treatment is to relieve the symptoms, while symptomatic remission is directly related to the quality of life. In other words, health-related quality of life and patient satisfaction may be reasonable criteria for GERD. In this paper, we will discuss the individualized medicine of GERD.

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Key words: Gastroesophageal reflux disease; Heterogeneity; Individual difference; Individualized medicine; Health-related quality of life

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## 摘要

胃食管反流病(gastroesophageal reflux disease, GERD)的发病率无论在发展中国家还是发达国家均在逐渐升高, 尤其是北美和亚洲, 疾病谱包括糜烂性反流病或反流性食管炎或糜烂性食管炎、非糜烂性反流病(nonerosive reflux disease, NERD)和Barrett食管三个亚型. GERD的病因、发病机制、临床表现以及对治疗的反应均显示出高度的异质性或个体间差异, 特别是NERD和难治性GERD; 另外, 尽管生物医学、药学技术的研发和快速发展为GERD诊断及治疗提供了越来越多和先进的手段, 但仍有一部分患者远期疗效和生活质量的改善尚未达到理想目标. 以上因素决定了每一位GERD患者需要一种针对其本人各项医学特征的个体化管理策略及个体化诊疗. GERD的治疗目标是缓解症状, 而症状的缓解又直接与生活质量相关, 因此健康相关生活质量和患者的满意度可能成为评价GERD疗效的客观标准. 本文充分阐述了GERD的个体化诊疗.

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关键词: 胃食管反流病; 异质性; 个体差异; 个体化诊疗; 健康相关生活质量

**核心提要:** 胃食管反流病(gastroesophageal reflux disease, GERD)已成为全球性慢性疾病, 而且发病率在逐年升高, 患病人群在逐渐扩大. GERD的病因、发病机制、临床表现以及对治疗的反应均显示出高度的异质性或个体间差异; 与其他疾病重叠存在; 虽有当今丰富、高效的诊疗手段, 但仍有一部分患者的症状及生活质量未达到明显改善. 以上决定了GERD需要个体化诊疗, 为患者作出正确的诊断、提供正确的治疗方案, 从而达到预后改善和费用最小化的目的. 个体化诊疗将成为GERD领域未来的研究方向.

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## 0 引言

长期以来, 人们已经习惯了针对同一种疾病按照同样的方案、相同的剂量服用同样的药物. 但医学科学发展至今天, 人们逐渐认识到, 每种疾病在每一个个

体的病因、发病机制、临床表型、对药物治疗的反应、甚至预后方面都存在很大差异. 世界卫生组织指出, 21世纪的医学将由“疾病医学”发展为“健康医学”, 由集体治疗转为个体治疗. 医疗正在逐渐转向医学模式: 预防(predictive), 个体化(personalized), 早期(preemptive), 参与式(participatory)<sup>[1]</sup>. 个体化医学逐渐在医学实践中被深刻理解和接受, 其特点是由疾病的单一性趋向于复杂性, 由生物因素转向多因素, 由“人的疾病”转向“疾病的人”, 医学科学中, 疾病不再被作为主要研究对象, 而是将人类健康作为研究对象和研究实践, 即所谓的“个体化医学”、“个体化诊疗”. 个体化医学最初被定义和集中于分子诊断以及癌症和肿瘤相关疾病的靶向治疗<sup>[2]</sup>, 近年来, 个体化医学概念逐渐渗透到医学的各个领域. 然而, 对于消化系统疾病的个体化医学研究尚未深入. 胃食管反流病(gastroesophageal reflux disease, GERD)是一种非常复杂的疾病, 常与其他疾病重叠存在, 如嗜酸细胞性食管炎、贲门失弛缓症、消化不良以及功能性食管疾病. 美国胃肠病学学会最近提出了针对GERD不同表型的“个体化诊疗”, 认为个体化诊疗的目的是在正确的时间为正确的患者提供正确的照顾, 不仅要改善预后而且将费用最小化<sup>[3]</sup>. 对于GERD而言, 对患者的影响涉及与健康有关的生活质量(health-related quality of life, HRQOL)、工作能力、甚至睡眠质量、生活能力<sup>[4]</sup>, 人们对疾病的预防、康复以及HRQOL的认识和需求逐渐提高, 因此GERD的个体化诊疗将会受到更多重视.

## 1 危险因素的个体差异

**1.1 性别与年龄** GERD发病随年龄增长而升高, 且与性别和年龄相关, Barrett食管(Barrett esophagus, BE)及食管癌也是同样<sup>[5]</sup>. 老年GERD患者的症状更不典型, 症状更不严重, 但组织学损伤严重<sup>[6]</sup>, 而且临床表现常以报警症状为特征, 因此GERD在老年人群中容易被低估、误诊甚至漏诊, 需全面评估<sup>[7]</sup>. NERD及食管外症状在女性中常见, 而器质性疾病如ERD、BE、食管腺癌(esophageal adenocarcinoma, EAC)以及胃食管连接部腺癌在男性中则更常见<sup>[8]</sup>; NERD人群中GERD症状的出现频率较ERD更高. 男性的烧心症状更易获得改善<sup>[9]</sup>. 女性在治疗时与质子泵抑制剂(proton pump inhibitors, PPIs)剂量增加的需求相关<sup>[10]</sup>.

**1.2 遗传、种族及地域差异** GERD发病率, 北美为18.1%-27.8%, 南美27.8%, 欧洲8.8%-25.9%, 东亚2.5%-7.8%, 中东8.7%-33.1%, 澳大利亚11.6%<sup>[11]</sup>. 在亚洲, GERD症状频率也在升高<sup>[12]</sup>. 中国新疆维吾尔族GERD

发生率远高于汉族人群(35% vs 28%)<sup>[13]</sup>, 而且高于上述结果. 美国高加索人群与非洲裔美国人群的GERD发生率并无差异, 但后者具有持续较低的食管炎风险<sup>[14]</sup>. 约翰内斯堡尽管城市中黑人与白人的比例为5:1, 但黑人BE患者的比例仅为5%<sup>[15]</sup>. 尼日利亚医学生GERD发生率为26.3%, 其中NERD的比例超过了60%<sup>[16]</sup>.

1.3 生活方式和饮食习惯的个体差异 睡眠质量差或作息不规律及饮食习惯不良可导致食管蠕动功能下降、夜间唾液分泌减少、上食管括约肌压力下降、仰卧时TLESR事件增多, 最终促使夜间酸反流的发生<sup>[17]</sup>. 吸烟使唾液中碳酸氢盐分泌减少而引起LESP下降及酸清除时间延长, 使咳嗽或深吸气时腹内压突然升高从而导致酸反流事件增加<sup>[18]</sup>. 酒精、碳酸饮料、高脂肪饮食、肉类、可乐以及咖啡均与GERD发病率增高有关, 通过刺激胃酸分泌、增加夜间酸反流、削弱食管黏膜屏障功能及清除功能、降低LESP而导致GERD夜间烧心的发生<sup>[13,19]</sup>. 吸烟增加GERD发生率、反流症状的频率及严重程度, 影响HRQOL<sup>[20]</sup>.

1.4 疾病及药物 肥胖是GERD的独立危险因素, 而且与BE和EAC相关, 腹型或内脏型肥胖在男性中更为常见、而且白人男性较黑人男性更常见<sup>[21]</sup>, 较单纯性肥胖与GERD及EAC更加密切相关<sup>[22]</sup>. 腹型肥胖通过升高腹内压而促进GERD发生, 进而导致反流和食管裂孔疝(hiatal hernia, HH)的进展<sup>[23]</sup>. GERD与睡眠障碍之间存在相互影响, 睡眠剥夺可增强食管对酸的敏感性(食管高敏感, hypersensitive esophagus, HE), 反之, GERD通过使患者在夜间睡眠时多次觉醒而影响患者的睡眠质量<sup>[24]</sup>. 合并睡眠障碍的GERD患者更易出现夜间酸反流和EE. HH和肠易激综合征均可与GERD重叠<sup>[25]</sup>. 结缔组织病特别是硬皮病、慢性阻塞性呼吸系统疾病、神经系统疾病和妊娠中, GERD均具有较高的发病率<sup>[26]</sup>. 已证实有多种药物通过影响LESP和食管清除功能而导致GERD, 包括非甾体类抗炎药、抗胆碱能药、苯二氮卓类药物、钙通道阻滞剂、硝酸盐、β阻滞剂、茶碱、多巴胺、尼古丁、硝酸盐、茶碱、雌激素、孕酮、胰高血糖素和一些前列腺素类制剂<sup>[27,28]</sup>. 老年人糖尿病和帕金森病可影响食管动力和LES功能<sup>[7]</sup>.

## 2 病理生理和发病机制的个体差异: NERD和RGERD

2.1 NERD GERD是一种由多种因素共同作用和/或多种因素及多种机制相互作用所导致的疾病. ERD(约占30%)属于一类由酸反流引起的器质性疾病, 而NERD(约占70%)的发病机制极其复杂, 这两种机制可

能存在根本的区别, 因此EE与NERD属于GERD的不同表型<sup>[29]</sup>, 从病理生理学角度, NERD具有明显的异质性<sup>[30,31]</sup>. 食管pH及腔内阻抗监测可区别酸反流与非酸反流<sup>[32]</sup>, NERD的24 h阻抗pH监测可有以下表现: (1)真正NERD, 存在异常食管酸暴(即食管酸暴露), (2)HE, 食管酸暴正常、且阳性症状与酸(正常酸度、弱酸)或非酸反流(碱性反流、气反流等)或二者共同相关. 非酸反流和弱酸反流可能是NERD的亚型<sup>[33]</sup>, 反映出NERD的异质性特征<sup>[34]</sup>. 在传统TLESR的病理生理基础上, 近年研究发现, 滑动性HH和酸袋(餐后存在于近端胃的一个未缓冲的高酸区域, 在健康者和GERD患者中普遍存在)也参与了GERD的发生. 食管胃连接部(esophagogastric junction, EGJ)收缩综合压力和EGJ扩张性增加成为GERD发病机制的最新观点<sup>[7]</sup>.

2.2 难治性胃食管反流病 虽然PPIs是GERD初始治疗和维持治疗的最有效药物, 但仍有1/3的患者对标准剂量的PPIs仅部分应答或完全缺乏应答, 被认为难治性胃食管反流病(refractory GERD, RGERD)<sup>[35,36]</sup>. 大约25%的RE及50%的NERD患者属于RGERD. AGA将持续依赖PPI治疗的“PPI部分应答者”GERD定义为一个新的表型<sup>[3]</sup>. CYP2C19基因多态性是影响PPIs疗效的重要因素, 快代谢型(rapid metabolizer, RM)者的CYP2C19基因型被认为具有对PPI治疗难治性的高风险, 需要增加PPI剂量或改进/调整治疗方案<sup>[36,37]</sup>. 自RGERD被提出后, 相继出现了一些其他定义如“PPI耐药”、“PPI抵抗”、“PPI无应答”及“PPI失败”, 尚未统一命名, 但均被认为是RGERD的原因, 而且大部分存在于NERD人群中<sup>[38,39]</sup>. 由于以往研究结果均来自西方, 日本学者将PPI耐药的NERD定义为: 在服用双倍剂量的PPI(如雷贝拉唑 10 mg, 每日2次), 并尽可能排除酸反流后仍有持续性症状者, 建议这些患者将双倍剂量的PPI改为一次性顿服<sup>[40]</sup>. 导致PPI耐药的可能机制包括: (1)对各种刺激的感知增强, 如胃酸、食管扩张、电刺激、温度等, 也就是内脏高敏感, (2)食管黏膜完整性受损或细胞间隙增宽, (3)酸袋是PPI耐药GERD发病机制中的主要因素<sup>[41,42]</sup>. 在长期使用PPIs的过程中, 59%的GERD、40%的NERD以及40%合并食管外症状者, 在每天一次PPI治疗过程中会出现持续性反流症状, 被称为“PPI失败”<sup>[43,44]</sup>, 原因包括: 老年、男性、吸烟、依从性差、给药时间不当、BMI>25 kg/m<sup>2</sup>; 明确的发病机制包括: 弱酸/非酸反流、十二指肠胃反流、胃排空延迟、食管动力障碍、夜间酸突破(nocturnal acid breakthrough, NAB)、HH、HE、嗜酸性细胞性食管炎、残余酸反流、PPI生物活性下降、缺乏持续性酸抑



制、RM以及心理共病<sup>[34,45]</sup>。

### 3 临床表现的个体差异

GERD是包含上述所有多因素和多病理生理机制的不同元素的异质性疾病。因此, 首先GERD是一种动力障碍性疾病, 特征为食管括约肌和蠕动障碍; 其次, 由于食管的高敏感性而使它不可避免地涉及神经胃肠病学(外周和中枢机制); 第三, 它是一种酸-消化疾病或酸-相关疾病; 最后, 反流常合并HH, 在HH存在时TLESR发生率增高。这样就不难理解GERD的临床表现多样化和明显不同的表现。NERD患者的胃肠道症状(如消化不良症状群)较ERD患者更严重。女性烧心和食管外症状的频率和强度以及来自腹痛、消化不良和便秘等的腹部不适症状均高于男性, 而且对PPI治疗多表现为部分应答<sup>[46]</sup>。以酸为主要病因和发病机制的NERD患者, 对PPI治疗可产生成功应答, 然而弱酸反流的HE对抑酸治疗则不能成功应答<sup>[45]</sup>。在PPI维持治疗期间, NERD及RGERD患者的上消化道症状较ERD患者更严重<sup>[47,48]</sup>。另外, GERD患者可能会出现多种不典型症状, 或者食管外症状<sup>[49]</sup>。

### 4 GERD的个体化治疗

如上所述, 治疗策略包括生活方式调整、药物治疗(控制胃酸分泌、促动力剂、抗焦虑/抑郁状态)以及抗反流手术外科治疗。虽然PPIs是传统一线治疗药物、抗反流手术可纠正GERD的病理解剖学异常, 但这仍不能解决所有GERD的困扰。GERD的流行病学、病因、发病机制、临床表现的异质性决定了GERD的治疗需要体现高度的个体化, 而最好的个体化治疗方案应当是在对患者的性别、年龄、症状特征、食管功能、形态学异常、病理生理机制、反流类型以及反流物性质全面评估基础上而制定, 其后的维持治疗以及HRQOL评估也应包括在内。

**4.1 生活方式、饮食习惯的调整** 生活方式及饮食习惯调整为一线、基础治疗, 包括减轻体重(对于超重人群), 避免酒精、刺激性及碳酸饮料、柑橘汁、烟草产品、薄荷、咖啡以及洋葱等饮食<sup>[50]</sup>。其他措施包括避免过量食肉、减少脂肪摄入、睡眠时抬高床头、左侧卧位、餐后3h避免卧位<sup>[51]</sup>。肥胖者当BMI下降 $3.5 \text{ kg/m}^2$ 时, GERD的风险将会降低40%<sup>[52]</sup>, 减轻体重对于老年及严重GERD患者同样有效, 一方面可因降低腹内压而减轻反流<sup>[53]</sup>, 另一方面可改善睡眠质量从而减少睡眠障碍与GERD的相互促进作用。戒烟(对于吸烟人群)可减少GERD的发生, 减轻反流的严重程度, 改善HRQOL<sup>[20]</sup>。一项最新的系统性综述分析结果表明, 呼

吸训练可通过增强膈肌的力量强度而提高LESP, 并改善食管屏障功能, 因此是GERD的一种非手术、非药物方案的补充疗法, 特别对轻度GERD患者起到关键作用<sup>[54]</sup>。

**4.2 NERD及RGERD的药物治疗** 当出现对PPI治疗部分应答或PPI治疗失败时, 下一步可能需要优化治疗方案, 如调整PPI用法(更换另一种PPI、增加剂量、将给药时间分为早晚2次、联合一种PPI或其他药物), 确定是否按照正确的时间服药, 提高依从性。联合用药可以考虑促动力剂、 $\text{H}_2$ 受体阻滞剂( $\text{H}_2\text{RA}$ )、TLESR抑制剂等,  $\text{H}_2\text{RA}$ 也可用于轻度GERD、GERD的按需治疗以及复发性食管炎的维持治疗<sup>[55]</sup>。反流症状突出者可给予促动力剂及TLESR抑制剂。功能性烧心和胸痛者可给予针对内脏高敏感和警觉过度的神经调节剂及行为治疗<sup>[3]</sup>。对弱酸反流具有HE的NERD患者可考虑反流抑制剂或手术治疗<sup>[45]</sup>。需要强调的是, 依从性差、不按医嘱的正确时间用药以及不正确的诊断可能是影响抑酸效果的重要因素, 在出现PPI部分应答或无应答时, 应当重新评估诊断治疗的正确性, 并对治疗方案进行优化。一项最新研究发现, 接受长期PPI治疗的女性GERD患者, 对之前PPI的半剂量更易耐受, 表明女性患者在维持治疗期间可给予较低剂量的PPI, 因而在这些患者中降阶梯治疗更容易获得成功<sup>[56]</sup>。严重的滑动性HH( $>3 \text{ cm}$ )和病态肥胖是导致PPI无应答的另外两个病因, 疝修补加抗反流手术和胃旁路外科手术分别是解决这两个问题的优选方法<sup>[57]</sup>。海藻酸钠是一种多糖, 与水结合形成黏稠的胶质, 漂浮于胃腔, 起到黏膜保护作用。海藻酸钠与抗酸剂的复合制剂(Gaviscon)可能是一种潜在的选择性针对“酸袋”的有效性靶向措施<sup>[58]</sup>; 而且可显著延长酸袋与EGJ之间的距离、甚至在某些个体中消除酸袋; 另外, 还对 $\geq 3 \text{ cm}$ 的HH有效且减少酸反流, 是RGERD及NERD理想药物<sup>[59,60]</sup>。

三环类抗抑郁药(如去甲替林)、选择性5-羟色胺再摄取抑制剂(氟哌噻醇美利曲辛、氟西汀)、疼痛调节剂对可通过影响中枢神经系统的痛觉通路而改善食管高敏感性, RGERD、反流不相关症状具有显著改善作用<sup>[61]</sup>。氟哌噻醇为三环类抗抑郁药, 作用靶点为突触前膜的多巴胺自身调节受体, 增加突触间隙的多巴胺浓度, 美利曲辛可通过抑制突触前膜再摄取5-羟色胺与去甲肾上腺素, 增加突触间隙中单胺类递质浓度, 二者协同作用可消除抑郁障碍, 降低食管高敏感性, 改善GERD患者胸痛症状, 改善食管动力<sup>[62]</sup>。氟西汀对于RGERD可显著降低烧心症状发生频率, 且对HE症状改善有效。

性别在GERD症状知觉中起到很重要的作用, 了解

与性别相关的生物因素在GERD中的差异有助于提供分别针对男性和女性的更好治疗策略。比如激素替代具有针对食管癌的保护效应<sup>[8]</sup>。GERD食管外症状的应答率远低于NERD, 促动力剂可显著减少咽喉反流症状<sup>[63]</sup>, 液体海藻酸钠悬浮剂(Gaviscon<sup>®</sup> Advance)可显著改善咽喉反流的症状分数和临床表现<sup>[64]</sup>。

一些正在研发的新药将为GERD患者提供更多的治疗选择。速释(immediate-release)型PPIs如速释奥美拉唑、速释埃索美拉唑用于睡前口服而非晚饭前口服, 对NAB的控制作用优于传统PPIs<sup>[65]</sup>。替托拉唑和伊拉普拉唑的半衰期更长, 可延长抑酸时间和缩短NAB间期<sup>[66]</sup>。右兰索拉唑是一种双向延迟释放系统, 即可延长抑酸时间又可增强抑酸效应, 对于PPI耐药、PPI失败NERD、以及RGERD是理想选择<sup>[67]</sup>。阿唑拉唑钠(Azeloprazole Sodium)不受CYP2C19代谢的影响。阿托胺和普卢卡必利通过促进乙酰胆碱释放和抑制乙酰胆碱酯酶活性、以及减少TLESR、或者作为潜在的5-HT<sub>4</sub>受体激动剂而增强上消化道动力<sup>[68,69]</sup>。沃诺拉赞(Vonoprazan)是一种新型钾离子竞争性酸阻断剂, 不受CYP2C19代谢影响, 可促进胃肠道动力, 对于NERD、GERD的合并症状如便秘、上腹痛、恶心等具有显著改善作用<sup>[70]</sup>。西尼必利是一种双靶点的促动力药物, 可同时激动5-HT<sub>4</sub>受体和拮抗多巴胺D2受体, 促进乙酰胆碱释放, 进而促进全消化道动力, 是RGERD的另一种治疗药物, 而且可改善功能性消化不良及肠易激综合征相关症状<sup>[71]</sup>, 于2018年在我国上市。

**4.3 NERD及RGERD的外科治疗及内镜下治疗** 腹腔镜下胃底折叠术是一种传统外科手术治疗方法, 可有效减少所有类型反流事件的次数, 缓解非酸反流、弱酸反流患者的症状。适应证包括: (1)内科治疗无效; (2)GERD导致严重呼吸道疾病<sup>[72]</sup>; (3)不能耐受药物不良反应或长期用药; (4)重度GERD、并发Barrett食管或食管狭窄<sup>[73]</sup>, 但不适用于年轻和症状非常典型患者。磁性括约肌增强装置(LINX<sup>®</sup> Reflux Management System)可增强LES静息压, 减少反流, 可显著改善GERD-HRQOL, 减少PPIs用量, 减少并发症, 降低手术需求, 显示了安全性和远期疗效, 尤其适用于对PPI应答差、不能耐受PPI不良反应以及维持治疗失败者<sup>[74,75]</sup>。内镜下射频消融术(Endoscopic Radiofrequency Ablation, RFA)作为一种微创介入方法, 具有足够的安全性, 对烧心和食管外症状疗效更有优势, 可改善PPI依赖患者的GERD症状评分及HRQOL<sup>[76]</sup>。Plicator系统内镜下全层折叠术及经口无切口胃底折叠术(Transoral Incisionless Fundoplication, TIF)可使GEJ部位的功能得到恢复<sup>[77]</sup>, 减少食管酸暴时间、降低症状评分、减少

PPIs用量, 是TLESR突出患者的使用指征。对当前药物治疗无效时, 可以考虑腔内前胃底折叠术(Endoluminal Anterior Fundoplication)<sup>[78]</sup>。抗反流黏膜切除术(anti-reflux mucosectomy, ARMS)是近期提出的方法, 可显著改善患者的症状, 且可维持中短期疗效<sup>[79]</sup>, 似乎是不合并HH的RGERD最佳方法, 但有待于更多研究、长期研究证实。

## 5 特殊人群的管理

**5.1 孕期女性GERD的管理** 孕期女性的GERD发病率超过50%, 在妊娠期前3 mo为16.9%, 中间3 mo为25.3%, 最后3 mo为51.2%<sup>[80]</sup>。妊娠中期3 moLESP可降至正常值的33%-50%, 至后期3 mo进一步降低, 原因包括腹内压升高、孕酮水平升高、胃排空异常以及肠道传输减慢<sup>[81]</sup>。GERD影响孕期女性的HRQOL, 尤其是在晚期妊娠, 因此HRQOL可以作为这一人群的适当检测手段<sup>[82]</sup>。生活方式调整为孕期GERD的一线治疗。药物可选用海藻酸盐和硫糖铝以及钙-镁抗酸剂, 雷尼替丁特别推荐应用于子痫前期患者。对于上述药物治疗无效者, 在权衡母亲与胎儿之间的利弊后, 在妊娠期的前3 mo之后可给予除奥美拉唑(被FDA分级为C类)以外的PPIs(被FDA分级为B类)<sup>[83,84]</sup>。

**5.2 老年GERD患者的管理** 生活方式调整为老年GERD患者的基础治疗, 包括减轻体重、戒烟、避免饮酒, 饮食调整包括限制巧克力、柑橘类水果和果汁、碳酸饮料、辛辣食物、番茄制品、红酒、咖啡因以及夜间加餐<sup>[85]</sup>。抗酸剂如碳酸钙和碳酸氢钠等应用时需注意防止高钙血症和便秘。海藻酸盐在胃腔内产生泡沫, 形成一种生理性屏障, 从而限制胃酸反流入食管, 对于咽喉反流患者有效, 也可用于需长期抗反流患者的管理<sup>[64]</sup>。PPIs是一线药物, 但需注意长期应用可能导致的不良反应和风险, 如痴呆、钙磷代谢异常、肠道菌群失调、社区获得性肺炎等<sup>[86]</sup>。H<sub>2</sub>RAs是二线药物, 主要用于NAB或最佳PPI治疗方案中不完全应答者。促动力剂如5-HT<sub>4</sub>受体激动剂与PPIs或H<sub>2</sub>RAs联用效果可能优于单药治疗<sup>[87]</sup>。传统治疗对症状控制不完全的患者, 手术治疗是其指征<sup>[76,77]</sup>。

**5.3 儿童和青少年GERD的管理** 婴幼儿的胃食管反流(GER)很常见, 尤其是在出生后6 mo内。在婴幼儿出生后的6 mo之内GER发生率很高(55%-73%), 1岁之后逐渐下降(4%-12%)<sup>[88,89]</sup>。儿童及青少年的GERD发生率较低, 美国报道3-9岁儿童及10-17岁青少年的发生率为1.8%及3.5%, 远低于成人<sup>[90]</sup>。随着年龄增长, GERD发病率缓慢上升。大部分健康婴儿会有每日的反食或呕吐, 并不影响正常生长, 属于生理性反流, 而GERD常与

表 1 GERD的个体化管理策略

管理方案	治疗措施
生活方式/饮食习惯调整	抬高床头,睡眠时左侧卧位 避免餐后3 h内卧床,避免睡前3 h进餐 肥胖、超重者减轻体重 避免烟酒、巧克力、柑橘类水果/果汁、番茄制品、薄荷、咖啡、洋葱
药物治疗	抗反流综合物理治疗,如呼吸训练 PPIs及优化PPIs治疗 H <sub>2</sub> RAs TLESR抑制剂 海藻酸盐(Gaviscon® Advance)/海藻酸盐-抗酸剂复合制剂 三环类抗抑郁药,选择性血清素再摄取抑制剂 新型PPIs和钾竞争性酸阻滞剂、促动力剂
内镜下腔内抗反流技术	内镜下射频消融术(RFA) 经口无切口胃底折叠术(TIF) 腔内前胃底折叠术
外科治疗	抗反流黏膜切除术(ARMS) 胃旁路手术/胃束带术 腹腔镜下胃底折叠术 磁性括约肌增强装置(LINX® Reflux Management System) 超声外科内支架术(MUSE)

GERD: 胃食管反流病; PPI: 质子泵抑制剂.

表 2 特殊人群GERD的个体化管理策略

GERD人群	管理方案及治疗措施
NERD, RGERD, PPIs部分应答, PPIs 提高依从性; 优化治疗方案, 如调整PPI的用法(种类、剂量、给药时间、联合一种PPI或其他药物), 与促动力剂或 耐药/PPIs失败	重新评估病因、发病机制及诊断; H <sub>2</sub> RAs/TLESR抑制剂联用; 功能性烧心、HE和胸痛者: 神经调节剂及行为治疗, 三环类抗抑郁药和选择性血清素再摄取抑制剂; 新型药物: 右兰索拉唑, 沃诺拉赞, 海藻酸钠-抗酸剂复合制剂(Gaviscon)(选择性针对“酸袋”的有效性靶向措施); 上述治疗无效: 内镜下治疗或手术治疗(参见表1).
妊娠期女性	生活方式调整为一线治疗; 海藻酸盐, 硫糖铝, 钙-镁复合抗酸剂; 雷尼替丁对先兆子痫者特别推荐使用;
老年患者	当对上述方案无应答时, 可以使用除奥美拉唑以外的其他PPIs. 生活方式调整为基础治疗, 对发作性烧心及反流症状效果明显; 减轻体重、戒烟、避免饮酒, 限制巧克力、柑橘类水果和果汁、碳酸饮料、辛辣食物、番茄制品、咖啡因、夜间加餐; PPIs是一线用药, H <sub>2</sub> RAs和抗酸剂为二线用药, 促动力剂与PPIs或H <sub>2</sub> RAs联用效果优于单药治疗; 以上方案对症状控制不佳者, 选择手术治疗.
儿童及青少年患者	以综合保守治疗措施为主; 婴儿期: 父母教育和支持, 减少喂食, 左侧卧位体位, 饮食浓稠, 不建议用PPIs; 生活方式调整: 儿童期: 超重/肥胖者减重, 避免咖啡因、巧克力 青少年: 避免酒精、烟草, 睡眠时左侧卧位+抬高床头; 药物治疗: PPIs为首选、至少12 wk. 右兰索拉唑可有效改善NERD患者的烧心症状及生活质量; 抗酸剂仅用于短期内的症状缓解; 外科手术治疗指征: 最佳治疗方案失败, 疗程较长、产生药物依赖, 以及出现危及生命的GERD并发症. 神经功能受损者最常需要手术.

GERD: 胃食管反流病; PPI: 质子泵抑制剂; RGERD: 难治性胃食管反流病; HE: 食管高敏感.



生长迟缓和/或食管炎有关, 如易激惹、喂食困难、入睡困难、哭闹和贫血; 也可有食管外症状以及很少见的呼吸暂停或明显危及生命的事件, 少儿(<12岁)常表现为恶心、呕吐、腹痛、厌食与拒绝食物, 年长儿童通常表现为与成人类似的症状, 以及食管外症状<sup>[91]</sup>. 部分儿童的解剖学异常(修补术后的HH及食管闭锁)及神经发育问题是发展为严重GERD的高危因素<sup>[92]</sup>. 青少年时期的GERD与成人哮喘正相关<sup>[93]</sup>, 儿童时期的肥胖及青少年时期的持续GER症状均与成人GERD发生风险增高相关. 儿童和青少年GERD的管理以综合保守措施为基础, 包括生活方式和饮食习惯调整、药物治疗以及少数的外科治疗<sup>[94]</sup>. 婴儿期最重要的管理是父母教育和支持、咨询, 其他措施包括喂食建议、体位和饮食浓缩、减少喂食量等, 左侧卧位有助于预防反流, 不建议用PPIs<sup>[95]</sup>. 儿童期GERD需要强效抑酸、疗程至少12 wk. PPIs是抑酸作用最强而且最有效的药物, 优于H<sub>2</sub>RAs<sup>[96]</sup>, 目前各种PPIs均可使用. 右兰索拉唑可有效改善青少年NERD患者的烧心症状及生活质量, 耐受性好<sup>[97]</sup>. 抗酸剂仅用于短期内的症状缓解. 外科手术治疗的指征为: 最佳治疗方案失败, 疗程较长、产生药物依赖, 以及出现危及生命的GERD并发症. 神经功能受损者最常需要手术, 但倾向于发展为外科相关并发症及手术失败<sup>[95]</sup>.

上述个体化管理方案包括生活方式调整、药物治疗、外科治疗归纳为表1, 特殊人群的管理见表2.

GERD症状的缓解直接与HRQOL相关<sup>[98]</sup>, 因此患者的满意度和HRQOL是一个评估GERD治疗成功与否的有用终点指标<sup>[99]</sup>, 也体现了个体化诊断和治疗过程中医疗质量的真谛. 综上所述, GERD因其复杂而异质性的病理生理机制及临床特征, 对临床诊疗提出了高度个体化的要求. 因此, 对每一位疑似GERD患者, 如果进行全面评估, 作出正确的、个体化诊断, 从而为患者提供正确的、个体化的最适管理方案, 那么改善预后、费用最小化、提高HRQOL将成为成本最低而收益最高的目标, 应成为评估GERD个体化诊疗的标准.

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