

世界华人消化杂志®

**WORLD CHINESE
JOURNAL OF DIGESTOLOGY**

Shijie Huaren Xiaohua Zazhi

2018 年 5 月 28 日 第 26 卷 第 15 期 (Volume 26 Number 15)



15/2018

ISSN 1009-3079



《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被美国《化学文摘(Chemical Abstracts, CA)》, 荷兰《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》和俄罗斯《文摘杂志(Abstract Journal, AJ)》数据库收录.



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世界华人消化杂志

Shijie Huaren Xiaohua Zazhi

吴阶平 题写封面刊名

陈可冀 题写版权刊名

(旬刊)

创 刊 1993-01-15

改 刊 1998-01-25

出 版 2018-05-28

原刊名 新消化病学杂志

期刊名称

世界华人消化杂志

国际标准连续出版物号

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

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Baishideng Publishing Group Inc

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Fax: +1-925-223-8242

Telephone: +1-925-223-8243

E-mail: wjgd@wjgnet.com<http://www.wjgnet.com>

出版

百世登出版集团有限公司

Baishideng Publishing Group Inc

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Fax: +1-925-223-8242

Telephone: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com<http://www.wjgnet.com>

制作

北京百世登生物医学科技有限公司
100025, 北京市朝阳区东四环中路
62号, 远洋国际中心D座903室

电话: 010-85381892

传真: 010-85381893

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被美国《化学文摘(Chemical Abstracts, CA)》、荷兰《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、俄罗斯《文摘杂志(Abstract Journal, AJ)》数据库收录.

《世界华人消化杂志》正式开通了在线办公系统(<https://www.baishideng.com>), 所有办公流程一律可以在线进行, 包括投稿、审稿、编辑、审读, 以及作者、读者和编者之间的信息反馈交流.

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定价

每期90.67元 全年36期3264.00元

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Indexed/Abstracted by

Chemical Abstracts, EMBASE/Excerpta Medica, Abstract Journals, and Scopus.

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Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993

Renamed on January 25, 1998

Publication date May 28, 2018

NAME OF JOURNAL

World Chinese Journal of Digestology

ISSN

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

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PUBLISHER

Baishideng Publishing Group Inc

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Fax: +1-925-223-8242

Telephone: +1-925-223-8243

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PRODUCTION CENTER

Beijing Baishideng BioMed Scientific Co., Limited Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China

Telephone: +86-10-85381892

Fax: +86-10-85381893

PRINT SUBSCRIPTION

RMB 90.67 Yuan for each issue

RMB 3264 Yuan for one year

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收稿日期: 2018-04-10

修回日期: 2018-05-11

接受日期: 2018-05-16

在线出版日期: 2018-05-28

Reflux hypersensitivity

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Received: 2018-04-10

Revised: 2018-05-11

Accepted: 2018-05-16

Published online: 2018-05-28

Abstract

Reflux hypersensitivity (RH) is a condition characterized typically by heart burn, normal gastroscopy and esophageal biopsy, normal esophageal pH-impedance test, and a close correlation between heart burn and reflux events. Recently, Rome IV criteria suggests that reflux hypersensitivity is a new type of esophageal functional disease. It is very common in clinical practice and often coexists with functional heartburn. Diagnosis is based on heartburn symptoms, gastroscopy, esophageal

biopsy, esophageal pH-impedance, and high resolution esophageal pressure. RH patients have normal acid exposure, and there is no dynamic disease in esophageal dynamic test. However, there are still some difficulties in the differential diagnosis of esophageal functional diseases. Symptom associated probability cannot reliably distinguish reflux hypersensitivity and functional heartburn. The pathogenesis of RH is not entirely clear. Recent studies have shown that esophageal sensitivity to acid and mucosal integrity can lead to RH. Because more than 90% of patients do not respond to proton pump inhibitors, esophageal neuromodulators, such as tricyclic antidepressants, are the main treatment, but the efficacy is uncertain. Surgery is a desirable method, but the indications should be strictly selected. In the future, it is important to strengthen the research of RH pathogenesis and seek new therapeutic targets.

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Key Words: Functional esophageal disease; Heartburn; Reflux; Reflux hypersensitivity; pH-impedance monitoring; Esophageal pressure measurement; Esophageal mucosal integrity; Neuromodulators

Chi ZC. Reflux hypersensitivity. *Shijie Huaren Xiaohua Zazhi* 2018; 26(15): 885-891 URL: <http://www.wjgnet.com/1009-3079/full/v26/i15/885.htm> DOI: <http://dx.doi.org/10.11569/wcjd.v26.i15.885>

摘要

反流高敏感(reflux hypersensitivity, RH)是指患者有典型的烧心症状, 胃镜检查 and 食管活检正常, 食管 pH-阻抗试验正常, 患者的烧心和反流事件之间密切相关. 新近Rome IV提出RH是新的一种食管功能性疾病, 临床上极常见, 并常与功能性烧心并存, 多发生在年轻人和中年妇女, 常与另一种功能性胃肠

病重叠,常伴有心理障碍和精神因素.诊断依靠烧心症状、胃镜、食管活检、食管pH-阻抗和高通量分辨率食管测压. RH与非糜烂性反流病(non-erosive reflux disease, NERD)和胃食管反流病不同, RH为正常酸暴露,食管动力试验无动力疾病存在. 但食管功能性疾病之间的鉴别诊断尚存不少难点. 症状相关概率并不能可靠区分RH与功能性烧心. 有关RH的发病机制尚不完全明了. 近年研究证实食管对酸敏感与黏膜完整性破坏可导致RH发生. 因90%以上患者对质子泵抑制剂无反应,因此,治疗主要用食管神经调节剂,如三环抗抑郁药,但疗效尚难肯定,反流手术是一个可取的方法,但应严格选择适应证. 今后应加强RH发病机制的研究,寻求新的治疗靶,具有重要的临床意义.

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关键词: 功能性食管疾病; 烧心; 反流; 反流高敏感; pH-阻抗监测; 食管测压; 食管黏膜完整性; 神经调节剂

核心提要: 反流高敏感(reflux hypersensitivity, RH)是新近提出的一种新的功能性疾病,烧心时正常内镜出现在非糜烂性反流病(non-erosive reflux disease, NERD)和功能性烧心两种情况, NERD为异常酸暴露,有阳性症状或阴性症状伴反流,若正常酸暴露,阴性症状伴反流称为功能性烧心,若正常酸暴露,阳性症状伴RH. 这是从Rome II、III逐步演变过来的概念. RH的提出显示人们对食管功能性疾病认识的进步与提高,使诊断更为精准与合理. 随着人们对不同类型食管功能性疾病发病机制异同的了解,提出了新的治疗策略,如NERD是由异常酸暴露所致,用质子泵抑制剂(proton pump inhibitor, PPI)治疗有反应;而功能性烧心和RH则由正常酸暴露对酸敏感所致,90%以上患者对PPI无反应,因此,目前治疗主要用食管神经调节剂,然而疗效并不理想,因此,有望新的治疗策略问世. 新近研究证实食管对酸敏感和黏膜完整性破坏可导致RH发生. 今后需加强RH发病机制的研究,以寻求更多新的且有高效的治疗方法,拭目以待.

池肇春. 反流高敏感. 世界华人消化杂志 2018; 26(15): 885-891 URL: <http://www.wjgnet.com/1009-3079/full/v26/i15/885.htm> DOI: <http://dx.doi.org/10.11569/wjcd.v26.i15.885>

0 引言

通过多年研究的不懈努力,食管功能性疾病已由4种增加到5种,即功能性胸痛、功能性吞咽困难、功能性烧心、贲门病和最新提出的反流高敏感(reflux hypersensitivity, RH). Rome II提出烧心和正常内镜包含非糜烂性反流病(non-erosive reflux disease, NERD)(异常

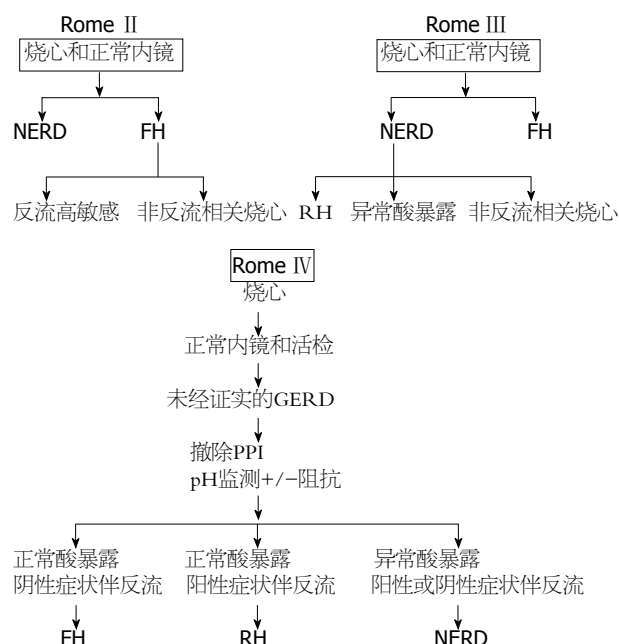


图1 功能性烧心、反流高敏感、非糜烂性反流病演变过程. NERD: 非糜烂性反流病; FH: 功能性烧心; RH: 反流高敏感; GERD: 胃食管反流病; PPI: 质子泵抑制剂.

食管酸暴露)和功能性烧心(正常食管酸暴露),后者又分为RH(食管高敏感)和非反流相关烧心2种^[1]. Rome III提出把NERD分为3个亚型,即RH、NERD(异常酸暴露)和非反流相关烧心,对质子泵抑制剂(proton pump inhibitor, PPI)有反应^[2]. 这样把RH从NERD中分出,致使NERD病例明显减少. Rome IV提出RH是一种新的食管功能性疾病^[3]. 并提出功能性烧心(functional heart, FH)或RH常与胃食管反流病(gastroesophageal reflux disease, GERD)重叠^[4]. 图1介绍RH从Rome II至Rome IV的演变过程^[5].

本文主要从食管功能性疾病分类入手,重点就RH的最新发病机制、诊断与鉴别诊断及治疗作一全面介绍,与广大读者共享.

1 流行率

有关RH的人群发病率目前尚无详细报道. 研究证明,烧心患者内镜检查,70%内镜检查正常,另30%内镜检查异常诊断为糜烂性食管炎. 内镜检查正常的烧心患者进一步进行pH试验,结果50%患者pH试验异常,诊断为NERD,另50%正常pH试验者,再测定症状指数,40%患者症状指数阳性,诊断为RH(占总烧心患者的14%);60%患者症状指数阴性,诊断为功能性烧心^[6].

新近几年研究用pH监测评价RH流行率. 内镜正常烧心患者撤除PPI治疗后用pH-阻抗监测,证实NERD占40%,功能性烧心占24%,RH占36%. Savarino等^[7]报道烧心患者对PPI治疗失败时RH的流行率,结果RH为28%,39%为FH,并发现RH时由酸反流所致者并不多

见. Patel等^[8]报告266例难治性烧心患者症状相关概率(symptom association probability, SAP)阳性者可分酸反流、弱酸反流或两者三种情况, 结果酸反流仅占6.5%, 弱酸反流占50.65%, 酸反流+弱酸反流占42.86%. 由此可见, RH患者仅少数由酸反流引起.

2 发病机制

与其他功能性疾病相似, 食管高敏感的发病机制与功能性胸痛和功能性烧心相似, 包括周围和(或)中枢神经系统敏化作用导致食管高敏感. 中枢神经对内脏刺激的处理过程异常和自主神经改变, 以及精神心理异常等机制有关. 在一个研究证明RH组对酸灌注或气球扩张时有化学或机械受体敏感性增加^[9].

近年研究证实, 食管黏膜屏障完整性破坏和食管对酸敏感性增高是发生食管高敏感的重要机制. 在食管RH患者中, 食管上皮细胞间隙和炎症趋化因子通过有害质子导致黏膜屏障受损, 进而使黏膜下层的神经末梢敏化. 在食管酸暴露的情况下酸敏感受体包括瞬时受体电位香草酸受体1上调, 影响了随后的痛觉信号传导. 食管酸灌注液可以诱发食管高敏感, 这种高敏感不仅出现在直接酸暴露中的远端食管(原发性痛觉过敏)还出现在离酸暴露的远端食管, 其可能通过中枢敏化导致继发性痛觉过敏. RH和FH患者无效的食管动力、化学的清除能力和黏膜完整性降低与发病相关, 一旦中枢敏化作用建立, 即使停止刺激, 症状可持续存在^[10-13].

精神心理因素在RH发生中起重要作用. 研究发现, 在诱发的食管症状感知在精神心理应激情况下会被强化. 在心理应激时, 中枢介导的处理过程可改变自主神经系统的活性, 调节脊髓对疼痛信号的传导, 而外周肥大细胞脱颗粒可改变胃肠道黏膜通透性; 进而放大患者对生理刺激的敏感性. 此外, RH与惊恐障碍、焦虑和抑郁均明显相关^[9].

进一步研究证明, 中枢因子, 如应激、过度警觉的心理障碍和睡眠不好在增加食管内刺激的认知上发挥重要作用^[14]. 心理因子在功能性胃肠病重叠综合征的产生和加剧是一个重要的因子^[15]. 在GERD患者急性心理应激可增加食管内酸灌注的敏感性. 对酸感知反应增加是伴有对应激情感反应增大, 且此与食管黏膜有无破坏无关. 若由于新近日常生活中的压力(事件)可改变感知疼痛阈, 并使症状加剧^[16,17]. 自身急性应激可引起食管黏膜通透性增加和发生上皮内间隙扩大^[18,19].

以上这些机制显示应激、酸暴露和食管高敏感在产生反流症状中的复杂相互关系. 总之, RH基础发病机制包括食管刺激、过度警觉、中枢和自主神经改变、心理应激改变等导致食管高敏感^[20,21]. pH-阻抗研

究还发现, 食管对非酸反流以及在正常酸暴露下也可有食管高敏感^[22].

Savarino等^[7]用多通道pH-阻抗证明弱酸反流事件增加和近端反流发生率增高, 这是RH患者症状发生的主要原因. 相反, Tamura等^[23]报告在NERD患者比RH患者总的和近端酸反流事件有显著增高. 另一个研究用高分辨食管测压(high-resolution esophageal manometry, HREM)在NERD和RH之间进行比较, 两者HREM值相似, 但发现NERD比RH患者有更大的酸暴露时间, 且近端和远端酸反流事件、化学清除和黏膜完整性损伤也增加^[12]. 新近研究指出, RH比FH患者有明显的远端食管高收缩反应^[24].

关于酸敏感受体, 通过免疫染色指出, 在糜烂的食管黏膜瞬时受体电位香草酸-1(transient receptor potential vanilloid, TRPV-1)阳性的神经纤维增加. TRPV-1主要表达于感觉神经元及其纤维, 如背根神经节和三叉神经节, 并参与多种病理生理过程. 最新的分子生物学实验发现了两个磷酸化的新位点, 即Ser-502和Ser-800, 两者可使失活的TRPV-1通道重活化^[25-27]. 同时也证明NERD患者TRPV-1表达增加^[28]. 新近Yoshida等^[29]报告在RH患者食管高敏感与神经源性炎症释放P物质和神经激肽-1(neurokinin-1)受体表达增加有关, 其机制可能与伴有TRPV-1和蛋白酶激活受体2激活所致. 由此可见这些酸敏感受体参与了食管RH的发生.

3 诊断与鉴别诊断

RH的临床表现与功能性烧心患者的临床表现虽有差异, 但从临床症状上往往很难将两者区分. 单靠SAP也不能精确地区分功能性烧心与RH^[30]. 用患者症状的严重性或烧心的持续与否并不能把GERD和烧心相关功能性疾病作出鉴别^[31]. 更为诊断困难的是RH常与其他肠功能性疾病症状重叠^[17,32]. 一个新近的研究提出RH患者焦虑比FH患者多见^[33].

RH多见于女性, 嗜酒者多见, 食管裂孔疝发生率高, 约半数病例并存IBS. De Bortoi等^[34]报告女性占66.6%, 饮酒者39.0%, 47.7%患者伴有食管裂孔疝, 48.2%伴有IBS, 35.8%患者有焦虑, 4.1%伴幽门螺旋杆菌阳性, 上述这些情况的临床意义有待进一步研究.

Rome IV提出RH诊断标准^[17], 强调必须具备下列条件: (1)胸骨后症状: 包括烧心和胸痛; (2)内镜检查正常, 无嗜酸性食管炎导致该症状的证据; (3)缺乏食管动力疾病(食管失弛症、胃食管联结部流出道梗阻、远端食管痉挛、Jackhammer食管^[34]和缺乏收缩性); (4)有反流诱发症状的证据, 但食管pH或pH-阻抗监测显示食管酸暴露正常(对PPI治疗有效, 不排除RH诊断).

根据上述标准, 一个烧心或胸痛患者, 食管pH或pH-阻抗监测显示阴性, 对PPI治疗无反应患者应首先想到RH的可能. 对难治性烧心患者首先用内镜检查并作活检, 以排除嗜酸性食管炎, 如果内镜检查及活检正常将进行MII(多通道阻抗)-监测或无线胶囊监测. 如果患者有GERD阳性史, 内镜和(或)pH试验异常, 将进行PPI治疗, 如果患者无GERD史, 将是撤除PPI治疗. 如果患者为正常酸暴露, SAP阳性, 此时应作食管动力试验, 若无动力疾病诊断RH, 如果SAP阴性, 又无重要的动力障碍诊断功能性烧心.

由以上所述可知, RH的诊断依靠临床症状诊断很为困难, 主要通过内镜、食管活检、食管pH和pH-阻抗监测. Gaf等^[12]对FH和RH和健康志愿者(HVs)的食管动力试验进行了比较研究. 结果RH与HV和FH比较, RH显示IEM(无效食管运动)和碎片蠕动率增加, 总的暴露量增大, 总的近端和远端反流事件增加, 化学清除和黏膜完整性降低. 高通量测压和阻抗(HRIM)和MII/pH(24 h多通道腔内阻抗和pH测定)可正确区分RH和FH. 另一个研究报告NERD和RH有相似的HRIM, 但NERD比RH有更大的酸暴露时间, 近端和远端酸反流事件和化学清除及黏膜完整性损害增加^[35]. 阻抗基线水平降低与食管酸暴露增加密切相关^[36]. 酸灌注试验引起平滑肌高收缩反应发现RH高于FH^[24]. 但这些试验均不能证实结构改变或炎症异常^[37].

4 治疗

食管高敏感由于涉及消化、心理、精神等专业. 因此, 治疗时应多学科合作联手进行. 因为RH患者的症状由反流事件触发, 故抗反流治疗是一线治疗, 包括药物、内镜和手术干预. 饮食和生活方式改变在RH上的作用仍不明^[38,39]. 近年研究发现SAP阳性患者对PPI治疗无反应, 但用MII-pH监测证明持续非酸或酸反流患者用腹腔镜胃底折叠术治疗获得成功^[40]. 如能仔细选择患者, 手术抗反流治疗可使反流得到控制^[8]. 同样Broederst等^[41]报告腹腔镜胃底折叠术可戏剧性减轻酸和弱酸以及液体和混合反流的发生率. 也有报告症状改善率手术治疗效果高于药物治疗^[42]. 不管怎样对手术治疗的系统评价一直很少研究. 现代的治疗理念是尽可能避免手术治疗, 目前手术治疗仅在少数患者中进行.

对所有的食管功能性疾病均可用神经调节剂治疗, 它也是RH治疗的基石, 早已提出, 三环类抗抑郁药(tricyclic antidepressants, TCA)对食管功能性疾病控制食管疼痛有效, 然而直至目前为止却缺乏系统的研究评估.

Limsrivili等^[43]首次随机对照试验研究小剂量丙咪

嗪(imipramine)睡前服治疗RH有37.2%的患者症状减轻, 且发现RH和FH两者的疗效相似. 由于疼痛减轻使生活质量也获改善, 但意向分析不显示丙咪嗪与安慰剂之间有任何不同, 在减轻症状上RH或FH用丙咪嗪治疗也未见比安慰剂更有效. 此需要更多临床治疗病例对照研究后再作出结论. 通过研究作者提出以下几点认识: (1)对食管功能疾病患者小剂量三环类药物已足够; (2)当PPI无效时应撤除; (3)FH和RH之间的鉴别尚不明确^[44].

三环类抗抑郁药有丙咪嗪、地昔帕明、氯咪帕明(安拿芬尼)通过抑制神经元对释放于突触间隙的去甲基肾上腺素和5-HT再摄取而产生抗抑郁. 近年新出现的抗抑郁药有氟西汀(百忧解)、噻奈普汀(达体朗)、草酸艾司西酞普兰(米士普)、马来酸氟伏沙明(释兰)、盐酸马普替林(路滴美)、氢溴酸西酞普兰(喜普妙)、盐酸度洛西汀(欣百达)、盐酸艾拉法辛(怡诺思)等均可试用RH的治疗^[45].

目前对RH尚无新的药物治疗, 藻酸盐、促动力药为一过性降低食管括约肌松弛抑制剂, 对RH有一定治疗作用^[46].

选择性5-HT再摄取抑制剂(SSRIs)也对各种食管功能性疾病, 包括功能性胸痛、RH、NERD和难治性烧心上治疗有效^[47-51]. 在RH患者一个随机对照试验, 75例RH患者随机接受西酞普兰(citalopram)20 mg, 或安慰剂, 随访6 mo, 治疗组38.5%, 对照组66.7%患者存在烧心症状($P = 0.02$)^[52]. 研究显示在RH患者对控制烧心有效.

SSRIs仅有5-HT活性, 所以比TCA的毒副作用小, 且耐受也较好. SSRIs在食管功能性疾病时开始和最大剂量氟西汀10-80 mg/d, 帕罗西汀10-60 mg/d、西酞普兰10-40 mg/d, 舍曲林25-200 mg/d. 曲唑酮在RH上的治疗仍未阐明. 目前仅有万拉法辛(venlafaxine)的应用研究, 据报告对RH和癔球症有疗效^[5].

最后必须指出, RH的发病常与心理障碍有关, 故应重视患者的心理行为治疗, 要求患者打消顾虑, 消除思想压力, 放松紧张情绪, 改变生活方式, 注意生活起居, 适当参加户外运动, 增强体质, 提高抗病能力^[53,54].

5 总结

RH是新的一种食管功能性疾病, 其特征有烧心、胸痛、内镜阴性、正常酸暴露、pH正常, pH-阻抗正常、SAP阳性、食管动力试验无动力疾病. 从症状上RH与其他食管功能性疾病难以鉴别, 内镜、pH试验、pH-阻抗是主要的鉴别手段. 食管功能试验尽管可将RH和FH加以鉴别, 但并不能证明食管结构改变、动力或炎症

异常. 由于RH对PPI90%以上患者无反应, 故药物治疗主要选用神经调节剂即抗抑郁药的使用. 有关抗抑郁药的疗效尚需进一步大系列病例的随机临床对照研究. 今后应深入RH发病机制的研究, 以寻求提供更多新的治疗靶, 为提高疗效, 减轻患者痛苦和降低资源消费作出努力.

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编辑: 马亚娟 电编: 张砚梁



ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569 © 2018 Baishideng Publishing Group Inc.
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• 消息 •

《世界华人消化杂志》性质、刊登内容及目标

本刊讯 《世界华人消化杂志》[国际标准刊号ISSN 1009-3079 (print), ISSN 2219-2859 (online), DOI: 10.11569, *Shijie Huaren Xiaohua Zazhi/World Chinese Journal of Digestology*], 是一本由来自国内31个省、市、自治区、特别行政区和美国的1040位胃肠病学和肝病学专家支持的开放存取的同行评议的旬刊杂志, 旨在推广国内各地的胃肠病学和肝病学领域临床实践和基础研究相结合的最具有临床意义的原创性及各类评论性的文章, 使其成为一种公众资源, 同时科学家、医生、患者和学生可以通过这样一个不受限制的平台来免费获取全文, 了解其领域的所有的关键的进展, 更重要的是这些进展会为本领域的医务工作者和研究者服务, 为他们的患者及基础研究提供进一步的帮助。

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ISSN 1009-3079

