

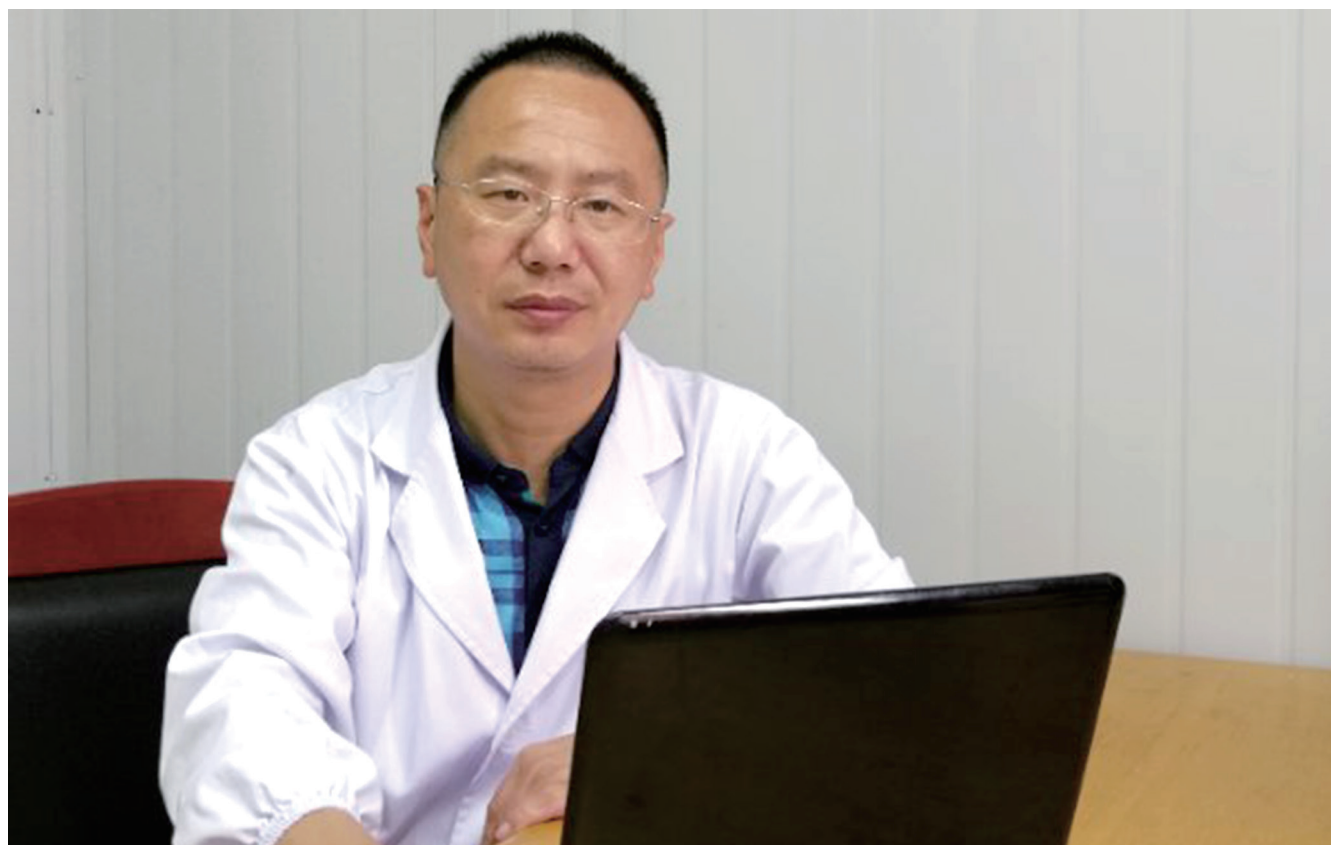
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高剂量双联疗法作为幽门螺杆菌感染根除方案的研究进展

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Progress in research of high-dose dual therapy as an eradication protocol for *Helicobacter pylori* infection

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Abstract

As antibiotic resistance rates increase, *Helicobacter pylori* (*H. pylori*) eradication regimens are constantly being updated. Quadruple therapy with bismuth is currently

the main empirical eradication regimen. However, long-term use of multiple antibiotics will enhance the resistance to them. Therefore, there is a need for a new regimen to eliminate *H. pylori* and reduce antibiotics used to prevent further resistance. High-dose dual therapy (HDDT) with a proton pump inhibitor and amoxicillin may be a breakthrough in eradicating *H. pylori*. Current research shows that HDDT, as a first-line regimen or rescue regimen, has an eradication rate comparable to quadruple therapy with a low incidence of adverse events, and the use of a single antibiotic greatly reduces the occurrence of antibiotic resistance.

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Key Words: *Helicobacter pylori*; High-dose dual therapy; First-line regimen; Rescue regimen

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摘要

随着抗生素耐药率不断的提高, 幽门螺杆菌 (*Helicobacter pylori*, *H. pylori*) 根除方案也在不断更新, 目前含铋剂的四联疗法是主要的经验治疗根除方案。但长期使用多种抗生素, 会增强其耐药性。我们需要一种能够根除 *H. pylori* 并减少所用抗生素的新方法, 以防止将来 *H. pylori* 产生抗药性, 而含质子泵抑制剂和阿莫西林的高剂量双联疗法 (high-dose dual therapy, HDDT) 可能是根除 *H. pylori* 的突破。目前研究表明, HDDT 作为一线治疗或者补救治疗, 其根除率与四联疗法相当, 不良事件发生率低, 而且使用单种抗生素大大减少了抗药性。

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关键词: 幽门螺杆菌; 高剂量双联疗法; 一线治疗; 补救治疗

核心提要: 在抗生素耐药性不断增长的时代, 含铋剂四联疗法的根除率也在逐步下降, 我们需要探索新的方案来提高根除率。21世纪以来, 国内外研究者对含质子泵抑制剂和阿莫西林的高剂量双联疗法(high-dose dual therapy, HDDT)做了许多的研究, 研究发现HDDT不论作为一线疗法还是补救治疗, 都有着较高的根除率, 且不良反应少, 很有潜力在临床上成为新的一线幽门螺杆菌根除疗法或补救疗法。

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0 引言

幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)是一种革兰阴性的微需氧菌, 全球约有一半以上的人口存在*H. pylori*的定植^[1]。流行病学研究显示, 不同地区的*H. pylori*感染率差异很大, 非洲(79.1%)、拉丁美洲和加勒比海(63.4%)、亚洲(54.7%)感染率居于前列^[2]。近来研究表明,*H. pylori*感染不仅与消化系统疾病密切相关, 也与冠心病、特发性血小板减少性紫癜、糖尿病、帕金森病等其他系统疾病有关。根除*H. pylori*可以改善胃炎、促进溃疡愈合、减少胃癌的发生^[3]。

由于抗生素耐药性、CYP2C19基因多态性、患者依从性等多方面因素, 标准三联疗法的根除率在逐步下降^[4]。2017年, 《马斯特里赫特V/佛罗伦萨共识报告》^[5]建议在克拉霉素耐药率高于15%至20%的地区放弃含质子泵抑制剂(proton pump inhibitors, PPIs)-克拉霉素的三联疗法, 推荐使用铋剂四联或非铋剂四联疗法; 在克拉霉素和甲硝唑双重耐药性较高的地区, 推荐使用铋剂四联疗法作为一线治疗。尽管这些方案都提供了可以接受的根除率, 但均含有2-3种抗生素, 可能会导致其耐药性增加, 同时也有研究报道四联方案的不良事件发生率更高^[6]。迄今为止, 已经研究了多种不同的改良治疗方案, 发现PPIs和阿莫西林的组合可能是一种可行的解决方案。Unge等^[7]在1989年就首次报道了双联方案以根除*H. pylori*, 随后世界各地学者研究了双联方案的不同设计, 发现标准剂量的PPIs和阿莫西林^[8]、单独增加阿莫西林或PPIs的剂量和给药频率^[9], 根除率均不高, 而同时增加PPIs和阿莫西林可以达到满意的效果^[10]。本文将就含PPIs和阿莫西林的高剂量双联疗法(high-dose

dual therapy, HDDT)的研究进展予以系统论述。

1 HDDT的简要介绍

HDDT主要包含PPIs和阿莫西林。阿莫西林是*H. pylori*治疗方案中的首选抗生素, 它具有良好的杀菌作用且耐药率很低。口服后, 它能够被迅速吸收到血浆中, 在6-8 h后排泄^[11]。为了维持尽可能高的阿莫西林血浆浓度, 建议每6 h给予500-750 mg。此外, 当胃内pH<6时, *H. pylori*处于非复制但可存活状态, 对阿莫西林具有表型抗性; 当pH>6时, *H. pylori*处于复制状态, 阿莫西林才能将其杀死^[12], 同时阿莫西林在较高的pH下更加稳定。PPIs是最常见的胃酸抑制剂, 主要在肝脏中被CYP2C19代谢。高剂量的PPIs或者增加PPIs的用药频率都可以使胃内pH维持在中性状态^[13]。但目前对于PPIs和阿莫西林的用药剂量和用药频率还未有统一的标准, 本文将以阿莫西林≥2.0 g/d, 阿莫西林或PPIs每天给药3到4次, 或阿莫西林和PPIs均每天给药4次, 持续14 d为HDDT的标准, 这与先前的研究一致^[14]。

2 HDDT作为根除*H. pylori*的一线治疗方案

研究发现, 在世界卫生组织的大多数地区, *H. pylori*对克拉霉素、甲硝唑和左氧氟沙星的耐药率均高于15%, 而阿莫西林不论原发性还是继发性耐药率都很低^[15]。因此, HDDT可能比现有的根除方案更有选择性优势(表1)。

早在二十世纪九十年代, 德国的一项多中心研究^[16]就报告了每天120 mg奥美拉唑和2.25 g阿莫西林的方案, 其*H. pylori*根除率约为90%, 是当时最有效的治疗方案之一。近10年来, 世界各地的研究者们不断探索, 其疗效也不尽相同。2012年韩国学者Kim等^[17]比较了HDDT (30 mg兰索拉唑和750 mg阿莫西林, 每天三次, 共14 d)和标准三联疗法的*H. pylori*根除率, 结果显示HDDT的根除率为78.4% (95%CI: 69.8%-86.9%), 根据根除*H. pylori*疗效分级标准来看, 该方案在韩国不能被接受。而日本^[18]、中国大陆^[19]的两项研究采用了10 mg雷贝拉唑和500 mg阿莫西林, 每天四次的方案, 均获得了90.0%以上的根除率, 更有中国台湾学者Yang等^[10]曾研究了20 mg雷贝拉唑和750 mg阿莫西林, 每天四次, 共14 d作为一线治疗的疗效, 获得了96.6% (95%CI: 93.7%-96.6%)的高根除率。此外, 2014年有学者Ren等^[20]就增加PPIs的剂量能否可以提高根除率这个问题进行了研究, R10A组给予雷贝拉唑10 mg bid和阿莫西林1 g tid, R20A组给予雷贝拉唑20 mg bid和阿莫西林1 g tid, 共14 d, 最终R10A组的根除率为80.0% (95%CI: 69.4%-90.6%), R20A组的根除率为93.0% (95%CI: 86.4%-99.6%), 可见增加PPIs的剂量而不增加抗生素的剂量可以提高*H. pylori*的根除率。

表 1 高剂量双联疗法作为根除幽门螺杆菌的一线治疗方案汇总

Ref.	地区	例数	PPIs	阿莫西林	疗程	不良事件(%)	根除率, <i>n/N</i> [% (95%CI)]		依从性(%)
							ITT	PP	
Bayerdörffer等 ^[16] , 1995	德国	136	奥美拉唑40 mg tid	750 mg tid	14 d	6.5	121/136 [89.0 (-)]	121/134 [90.3 (-)]	98.6
Graham等 ^[25] , 2010	美国	36	埃索美拉唑40 mg tid	750 mg tid	14 d	19.4	26/36 [72.2 (56-84)]	26/35 [74.2 (56-87)]	91.7
Kim等 ^[17] , 2012	韩国	104	兰索拉唑30 mg tid	750 mg tid	14 d	18.3	70/104 [67.3 (58.3-76.3)]	69/88 [78.4 (69.8-86.9)]	<80
Ren等 ^[20] , 2014	中国大陆	58	雷贝拉唑10 mg bid	1000 mg tid	14 d	9.1	44/58 [75.9 (64.9-86.9)]	44/55 [80.0 (69.4-90.6)]	-
		59	雷贝拉唑20 mg bid	1000 mg tid	14 d	10.5	53/59 [89.8 (82.1-97.6)]	53/57 [93.0 (86.4-99.6)]	-
Zullo等 ^[29] , 2015	意大利	56	埃索美拉唑40 mg tid	1000 mg tid	10 d	8.9	49/56 [87.5 (78.8-96.2)]	49/54 [90.7 (-)]	100
Kwack ^[30] , 2016	韩国	29	艾普拉唑40 mg bid	750 mg qid	14 d	10.3	23/29 [79.3 (61.6-90.2)]	23/28 [82.1 (64.4-93.2)]	96.6
Yang等 ^[10] , 2016	中国台湾	150	雷贝拉唑20 mg qid	750 mg qid	14 d	15.5	143/150 [95.3 (91.9-98.8)]	143/148 [96.6 (93.7-99.6)]	98.6
Hu等 ^[31] , 2017	中国大陆	87	雷贝拉唑10 mg qid	750 mg qid	14 d	3.4	68/87 [78.1 (68.4-86.8)]	68/86 [79.1 (70.5-87.7)]	98.9
		87	雷贝拉唑20 mg qid	750 mg qid	14 d	5.7	71/87 [81.6 (73.5-89.7)]	71/85 [83.5 (75.6-91.4)]	97.7
Sapmaz等 ^[32] , 2017	土耳其	98	雷贝拉唑20 mg tid	750 mg tid	14 d	-	84.7	84.9	90.8
Suo等 ^[19] , 2019	中国大陆	200	雷贝拉唑10 mg qid	500 mg qid	14 d	21.2	175/200 [87.5 (82.5-91.5)]	172/189 [91.0 (86.3-94.7)]	96.0
Yang等 ^[21] , 2019	中国大陆	116	埃索美拉唑20 mg qid	750 mg qid	14 d	6.3	102/116 [87.9 (82.0-93.9)]	102/112 [91.1 (85.5-96.4)]	96.6
Tai等 ^[26] , 2019	中国台湾	120	埃索美拉唑40 mg tid	750 mg qid	14 d	9.6	110/120 [91.7 (85.3-96.0)]	110/115 [95.7 (90.2-98.6)]	100
Yu等 ^[33] , 2019	中国大陆	80	埃索美拉唑40 mg bid	1000 mg tid	14 d	7.5	74/80 [92.5 (84.4-97.2)]	73/76 [96.1 (88.9-99.2)]	98.8
Öztürk等 ^[34] , 2020	土耳其	150	雷贝拉唑20 mg tid	1000 mg tid	14 d	0	137/150 [91.3 (-)]	137/144 [95.1 (-)]	96

PPIs: 质子泵抑制剂。

当前我国*H. pylori*根除方案主要推荐经验性铋剂四联方案, 目前已有HDDT与铋剂四联疗法比较的相关研究. 2019年中国的一项随机对照试验^[21]比较了埃索美拉唑(20 mg qid)联合阿莫西林(750 mg qid)方案与含铋剂四联方案, 结果显示双联方案的根除率为91.1% (95%CI: 85.8%-96.4%), 含铋剂四联方案的根除率为91.2% (95%CI: 86.0%-96.4%), 两者没有统计学差异. 在不良反应方面, 含铋剂四联方案组有26人发生了恶心、腹泻、皮疹、味觉消失等副作用, 而双联方案组只有7人发生了副作用, 总体不良反应显著降低. 近期的一项荟萃分析^[14]的结果也表明高剂量双联方案的根除率与含铋剂四联方案相似, 但铋剂四联方案的副作用更大.

可见, 对于初治患者来说, HDDT有着较高的根除率, 但研究结果各不相同, 需要更多的大数据研究证明.

3 HDDT作为根除*H. pylori*的补救治疗方案

据流行病学统计, 抗生素的耐药率不断提高^[15], 尤其在高耐药地区, *H. pylori*的根除率在不断下降, 这时就需要进行补救治疗.

在大多数的研究中, HDDT在补救治疗方面与三联方案一样安全、有效. 一项来自中国台湾^[10]的前瞻性随机试验研究了在*H. pylori*根除失败后, HDDT组(雷贝拉唑20 mg qid联合阿莫西林750 mg qid)和三联疗法组的根除率, 结果显示, HDDT组的根除率为89.3% (95%CI: 80.9%-97.6%), 三联疗法组的根除率为78.6% (95%CI: 67.8%-89.7%), 且HDDT的不良反应更少. 来自日本的两项研究报告了标准三联疗法失败后, 用雷贝拉唑10 mg qid和阿莫西林500 mg qid, 共14 d进行补救治疗的疗效, 最终都获得了不错的根除率, 分别为93.8% (95%CI:

84.8%-98.3%)^[22]、86.9% (95%CI: 66.4%-97.2%)^[23]。此外, 与铋四联疗法相比, HDDT也有着相同的疗效。德国的一项多中心试验^[24]研究表明, 高剂量奥美拉唑和阿莫西林的双重疗法和铋四联疗法均能有效且安全的根除对甲硝唑和克拉霉素均耐药的*H. pylori*感染。

4 目前研究的局限性

4.1 普适性不高 虽然当前HDDT的随机对照试验很多, 但研究结果不一, 甚至采用相同的方案在不同的地区结果也不尽相同, 如美国研究者Graham等^[25]以埃索美拉唑40 mg tid和阿莫西林750 mg qid为研究, 获得了74.2% (95%CI: 56%-87%)的根除率, 但台湾Tai等^[26]以相同方案却得到了95.7% (95%CI: 90.2%-98.6%)的根除率。这很有可能是由于地区、人群的差异性。第一, 不同地区对抗生素的耐药率不同。在该疗法中阿莫西林是最主要的杀菌剂, 故在Tai的研究中对阿莫西林耐药率为0的人群获得了普遍较高的根除率。第二, CYP2C19基因型状态存在种族差异。与亚洲人(30%-40%)相比, 高加索人(70%-75%)的RM基因型频率更高^[27]。因此, 临床医生需要根据患者的CYP2C19基因型状况, 选择合适的PPIs进行最佳治疗。另外, 目前的大多数研究都是单中心研究, 这也使结果的普适性受到了影响。

4.2 难以监测胃内24 h pH值 HDDT最重要的就是要保持胃内pH>6, 使*H. pylori*进入复制状态, 提高对阿莫西林的敏感性。但由于实验条件限制, 很多研究都未能监测胃内pH值, 这样就不能提供PPIs给药频率的依据。

5 结论

尽管目前大多数研究表明HDDT作为一线治疗或补救治疗, 其根除率都很高, 而且不良事件的发生率较其他疗法普遍较低, 但目前的研究仍有不足之处, 接下来我们需在全球各地区做大量随机对照试验来验证其优越性、安全性、可行性。除此之外, PPIs的选择、两种药物的剂量和给药频率也仍需进一步研究, 以达到HDDT的最佳疗效。此外, 一种新型酸抑制剂-Vonoprazan引起了我们的关注, 这是一种钾竞争性酸抑制剂, 具有高效且长效的抑酸作用, 在联合阿莫西林根除*H. pylori*的研究中, 只需低剂量就能达到较高的根除率, 有可能成为未来根除治疗的首选^[28]。

综上所述, 在抗生素耐药不断增长的年代, HDDT很有潜力成为新的一线*H. pylori*根除疗法或补救疗法。

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