·综 述·

幽门螺杆菌多重耐药性对胃肠疾病诊治的挑战与应对策略

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摘 要：幽门螺杆菌(*Helicobacter pylori*)可引起慢性胃炎、胃十二指肠溃疡等疾病，被世界卫生组织列为I类致癌物。临床上主要用抗生素对*H. pylori*进行杀菌清除治疗。抗生素清除*H. pylori*不彻底引起的持续感染成为胃癌高发的潜在风险。随着抗生素的广泛使用，*H. pylori*产生了多重耐药(multidrug resistance, MDR)，进而引起慢性胃病治疗失败及耐药菌株传播风险增加。幽门螺杆菌的多重耐药已成为胃肠疾病诊治的严峻挑战之一。本文结合相关文献和课题组的研究结果，综述了*H. pylori*多重耐药的全球发展趋势、发生机制、对临床诊断的挑战以及对药物研发的挑战，提出了依据*H. pylori*的*cgt*基因表达量测定活菌的新方法，胞内化是*H. pylori*耐药的新形式，O-聚糖抗*H. pylori*是应对多重耐药的防治新策略。本文为深入理解*H. pylori*多重耐药的机制及其防治策略提供了新的思路，有望为未来临床治疗和抗菌药物研发开辟新方向。

关键词：幽门螺杆菌；多重耐药；胞内化；防治新策略

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Multidrug resistance of *Helicobacter pylori* and its impact on the diagnosis and treatment of gastrointestinal diseases and countermeasures

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Abstract: *Helicobacter pylori* is a bacterium that can cause chronic gastritis, peptic ulcers, and other gastrointestinal diseases. The World Health Organization has classified *H. pylori* as a group I carcinogen. Antibiotics are the primary clinical approach for eradicating *H. pylori*. However, incomplete eradication of *H. pylori* by antibiotics can lead to persistent infection, which is a major risk factor for the high incidence of gastric cancer. The widespread use of antibiotics has led to the emergence of multidrug resistance in *H. pylori*, contributing to treatment failures of chronic gastric diseases and increasing the risk of spreading resistant strains. Multidrug-resistant *H. pylori* has become a serious challenge in the diagnosis and treatment of gastrointestinal diseases. This paper reviews the global trends in the development of multidrug resistance in *H. pylori*, the underlying mechanisms, the challenges it poses to clinical diagnosis, and its impact on drug development, drawing on relevant literature and the research findings from our group. It proposes using *cgt* expression as a novel method for determining viable bacteria, identifying intracellularization as a new form of resistance in *H. pylori*, and exploring the potential of O-glycans as a therapeutic approach against *H. pylori* to address multidrug resistance. It provides new insights into understanding the mechanisms of *H. pylori* multidrug resistance and its prevention strategies, offering promising directions for future clinical treatments and antimicrobial drug development.

Keywords: *Helicobacter pylori*; multidrug resistance; intracellularization; new strategies for prevention and treatment

幽门螺杆菌(*Helicobacter pylori*)在 1982 年由 Barry Marshall 和 Robin Warren 首次发现，这 2 位科学家因此在 2005 年荣获诺贝尔生理学或医学奖[1]。目前，*H. pylori* 感染人数极高，全球感染率高达 50%，影响全球 44 亿人；耐药率高，在许多国家和地区，克拉霉素(clarithromycin, CLA)的耐药率超过 15%[2]；复发率高，全球平均复发率约为 13%[3]。*H. pylori* 感染已被广泛研究并证实其与多种胃部疾病密切相关，包括慢性胃炎、胃溃疡、十二指肠溃疡、胃癌以及胃黏膜相关淋巴样组织淋巴瘤等疾病[4]。除此以外，*H. pylori* 感染还可引发多种胃外系统性疾病，影响胃肠系统、血液系统、神经系统、代谢系统等多个系统[5-6]，引起共 10 余种疾病。2017 年世界卫生组织将 CLA 耐药性 *H. pylori* 列入了新型抗生素研发重点病原体清单，该名单包括了对人类健康构成最大威胁的 12 种细菌，其中包括万古霉素耐药屎肠球菌，甲氧西

林耐药、万古霉素耐药金黄色葡萄球菌和 CLA 耐药幽门螺杆菌等[7]。*H. pylori* 已成为全球科学研究的重点领域之一，其耐药性问题成为临床治疗中的重大挑战。

多重耐药(multidrug resistance, MDR)是指对 3 种以上不同类别的抗生素具有耐药性，这取决于地理区域、研究时间和患者的特征[8]。1997 年发布的共识报告(Maastricht I Consensus Report)提出每日 2 次服用克拉霉素(clarithromycin, CLA)、甲硝唑(metronidazole, MET)或阿莫西林(amoxicillin, AMX)和质子泵抑制剂(proton pump inhibitors, PPI)的三联疗法，这成为了临床标准治疗方法[9]。三联疗法作为治疗 *H. pylori* 的有效方法引起了新的临床问题，如 CLA 耐药性在许多国家迅速增加，在中国耐药率高达 50%[10]，土耳其耐药率约 40%，日本和意大利约 30%[11]，在瑞典的耐药率约为 15%[12]。原发性耐药是由于耐药菌株在宿主体外环境中传播，继发性耐药则是由于细菌在抗生素治疗中适应或突变而导致的。除美洲和东南亚地区的 CLA 原发性耐药率为 10%，欧洲地区的左氧氟沙星(levofloxacin, LEV)原发性耐药率为 11%外，其余所有世界卫生组织(World Health Organization, WHO)地区对 CLA、MET 和 LEV 的原发性和继发性耐药率均≥15%，全球范围内 *H. pylori* 的耐药性已达到令人担忧的水平[13]。全球耐药具体趋势如表 1 所示。

1 幽门螺杆菌多重耐药性产生机制

H. pylori 多重耐药性的产生有很多原因，包括抗生素滥用、治疗不规范、初始根除治疗失败等。对来自 18 个欧洲国家的 24 个中心的原发性抗生素耐药性的评估证实了社区大环内酯类和喹诺酮类药物消费与 *H. pylori* 耐药性之间呈正相关[29]。初始根除治疗失败是 *H. pylori* 多重耐药的另一个重要原因。意大利的一项回顾性研究显示，数个疗程治疗失败的患者 MDR 发生率为 74.2%，明显高于未治疗患者的 21.3%[30]。除此以外，*H. pylori* 多重耐药性产生的核心原因是细菌因素，如突变、外排泵和生物膜[31]以及胞内化引起耐药。具体如图 1 所示。

1.1 基因突变

随着 *H. pylori* 耐药机制研究的深入，基因突变引起了研究人员的关注。基因突变通过改变药物靶点或抑制细胞内的药物活化来破坏抗生素的细胞活性[31]。目前，关于 *H. pylori* 抗生素耐药性基因突变的研究非常丰富，已报道的大多数抗生素耐药性编码基因变化是突变(例如，错义、无义、移码、插入或缺失)，而不是基因获得或丢失(例如串联基因扩增或水平基因转移)[32]。*H. pylori* 与耐药性相关的基因突变情况如表 2 所示。

1.2 外排泵上调

H. pylori 中有 5 个外排转运蛋白家族[46]，包括 ABC、MFS、MATE、SMR 和 RND 家族[30]。特别是 RND 家族转运蛋白在外排泵中发挥重要作用，参与多种抗生素的外排，包括 CLA、AMX 和四环素(tetracycline, TET)[47]。具体来说，每个 RND 家族都由以下 3 个组成部分：内膜外排蛋白(inner membrane efflux protein, IEP)，周质外排蛋白(periplasmic efflux protein, PEP)，外膜外排蛋白(outer membrane efflux protein, OEP)[48]。OEP 编码基因 *hef A* 被证实是影响 RND 家族外排泵功能的关键基因。*hef A* 基因的过表达促进外排泵系统将抗生素外排，导致 MDR 的 *H. pylori* 菌株产生。

表 1 各国对幽门螺杆菌多重耐药率的汇总

Table 1 Summary of multidrug resistance rates of *Helicobacter pylori* in various countries

Location	Antibiotic combination	Resistance rate (%)	Reference
Beijing, China	MTZ+CLR	20.0	[14]
	LEV+CLR	2.5	
	MTZ+CLR+LEV	32.5	
	MTZ+CLR+AMX+LEV	5.0	
	MTZ+AMX+CLR	1.7	
Jiangsu, China	LEV+CLR	14.0	[15]
	LEV+AMX	1.0	
	LEV+AMX+CLR	1.0	
Guangxi, China	MTZ+CLR	25.0	[16]
	AMX+CLR	10.0	
	MTZ+TET	16.0	
Qingdao, China	CLR+LEV	10.4	[17]
	CLR+MTZ	7.5	
	CLR+LEV+MTZ	9.0	
The Republic of Korea	CLR+MTZ	6.1	[18]
	CLR+FQN	8.2	
	MTZ+FQN	8.2	
	CLR+AMX+FQN	8.2	
Mongolia	CHP+ERY	5.9	[19]
	MTZ+AMX	7.2	
	MTZ+ERY	4.6	
Malaysia	CLR+MTZ	56.5	[20]
Vietnam	CLR+MTZ+LEV	31.6	[21]
Thailand	CLR+MTZ	12.9	[22]
Iran	MTZ+OFX	4.6	[23]
	MTZ+OFX+CIP+LEV	6.4	
	MTZ+OFX+TET+CIP+LEV	5.0	
Turkey	CLR+MTZ+LEV	18.1	[21]
Bulgaria	CLR+MTZ+AMX	7.1	[21]
Portugal	CLR+MTZ	20.0	[24]
France	CLR+MTZ+CIP	4.8	[21]
Spain	CLR+MTZ+LEV	2.4	[21]
Italy	CLR+MTZ	21.9	[25]
	CLR+LEV	9.4	
	MTZ+LEV	13.4	
Germany	CLR+LEV	2.6	[26]
Israel	MTZ+CLR	28.6	[27]
Argentina	CLR+MTZ+LEV	7.7	[21]
Chile	CLR+MTZ	18.0	[28]
	CLR+LEV+MTZ	12.5	

MTZ：甲硝唑；CLR：克拉霉素；LEV：左氧氟沙星；AMX：阿莫西林；TET：四环素；GEN：庆大霉素；FZD：呋喃唑酮；ERY：红霉素；CST：粘菌素；CHP：氯霉素；CIP：丙环沙星；OFX：氧氟沙星；FQN：氟喹诺酮类。

MTZ: Metronidazole; CLR: Clarithromycin; LEV: Levofloxacin; AMX: Amoxicillin; TET: Tetracycline; GEN: Gentamicin; FZD: Furazolidone; ERY: Erythromycin; CST: Colistin; CHP: Chloramphenicol; CIP: Ciprofloxacin; OFX: Ofloxacin; FQN: Fluoroquinolones.

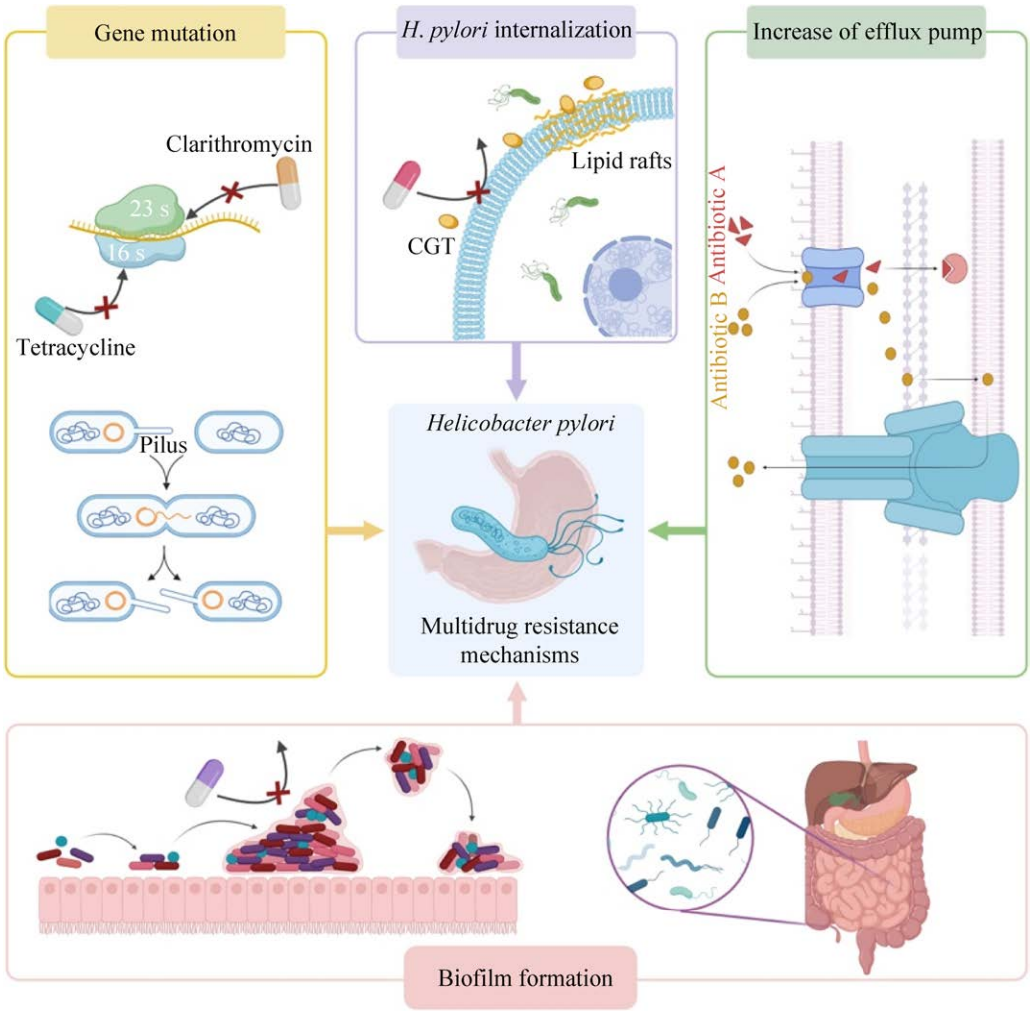

图 1 ***Helicobacter pylori* 的多重耐药发生机制** CGT：胆固醇-α-葡萄糖基转移酶。

Figure 1 Mechanisms of multidrug resistance in *Helicobacter pylori*. CGT: Cholesterol-α-glucosyltransferase.

1.3 生物膜形成

H. pylori 生物膜的形成也是 MDR 的重要机制[46]。生物膜是一种复杂的微生物生态系统，是与慢性感染相关的多维基质封闭细菌群落[48-49]。当这种生物膜存在并附着在细胞表面时，*H. pylori* 对多种抗生素的耐药性比相应的浮游状态高 100–1 000 倍[49]。在 *H. pylori* 形成的生物膜中，外排泵基因(比如 *HP0939*、*HP0497*、*HP0471* 和 *hef A*)的表达增强，已被证明与抗生素敏感性降低有关，并促进了 MDR[48]。

1.4 胞内化

2023 年本课题组对 *H. pylori* 的胞内化机制进行了深入探讨[50]，进一步提出了该感染机制对临床治疗中的挑战。*H. pylori* 胞内化可以引起抗生素抵抗[51]，导致感染宿主免疫逃逸[52]，抑制宿主细胞的自噬作用[53]。胞内化导致的临床症状往往表现为无症状或持续感染，未来可能增加发展为胃部严重疾病的风险。抗生素需在胞内达到足够浓度才能有效消灭 *H. pylori*，但当胞内药物浓度低于最低抑菌浓度时，不仅抑菌效果有限，反而可能形成选择性压力，促进耐药基因的产生和维持[54]。新发现的 *H. pylori* 毒力因子胆固醇-α-葡萄糖基转移酶(cholesterol-α-glucosyltransferase, CGT)由 *Hp0421* 基因编码，

表 2　幽门螺杆菌与耐药性相关的基因突变情况

Table 2　Gene mutations associated with drug resistance in *Helicobacter pylori*

Antibiotic type	Gene	Resistance mutations	Mechanism	Reference
β-lactams (eg, amoxicillin)	*pbp-1A*	S402G, E406A, S417T, S414R, T555S, N561Y	Interferes with cell wall synthesis	[33-35]
	pbp2	V312M, V313A, G353R		
	pbp3	F233L		
	pbp4	Y266H, Y267H		
	hofH	G22W	Increasing the efflux efficiency of efflux pumps	[36]
	hefA	–		
	hefC	D131E, L378F		
	hopC	R302H	It causes changes in membrane permeability	
Macrolides (eg, clarithromycin)	*23S rRNA*	A2142C/G, A2143G	Alteration affinity for the peptidyl transferase ring	[37-38]
	rpl22	226-228delGTG, T265-T266insTTCCATGIA	Synergistic effect with 23S rRNA V region mutations	[39]
	infB	G160A		
Nitrofurans (eg, furazolidone)	*porD*	G353A, A356G, C357T, C347T, C347G, C346A	Mutations cause amino acid changes	[40]
	oorD	A041G, A122G, C349A/G, A78G, A112G, A335G, C156T, C165T		
Fluoroquinolones (eg, levofloxacin)	*gyrA*	D192N, A199V/I, D86N, N87A/K/I/Y/T, A88N/P/V, H57Y, S63P, V651, V77A, S83A, A129T, R130K, D155N, D91G/N/A/H/Y, A92T, D99V, R103H, D161N, V172I, P188S	Affect the binding of DNA helicase to quinolone antibiotics	[41]
	gyrB	D435N, D481E, R484K, V437L, S429T, E463K, F438S, R579C	–	[37-38]
Nitroimidazoles (eg, metronidazole)	*rdxA*	R16H/C, M21A	–	[42]
	frxA	K20, Q164, K17, R13, A15, G165, R206	Reduces the ability of metronidazole to revert to its active form	[42]
	frxB	–		
Tetracyclines (eg, tetracycline)	*16S rRNA*	c.965-967delAGAinsTTC	Mutations within the TET binding site	[43-45]
Rifamycins (eg, rifabutin)	*rpoB*	V149F, Q524P, D530(V/E/N), V538I, H540(N/Y), L525P, Q527(K/R), S545L, A603T, I586(N/L)	This gene encodes the β subunit of RNA polymerase	

表中除大环内酯类(例如克拉霉素)、硝基呋喃类(例如呋喃唑酮)、四环素类(例如四环素)是核苷酸突变以外，其余均为氨基酸突变。

In the table, except for macrolides (such as clarithromycin), nitrofurans (such as furazolidone), and tetracyclines (such as tetracycline), which are nucleotide mutations, the rest are amino acid mutations.

在胆固醇糖基化中发挥多种功能，包括增强抗生素耐药性、维持天然螺旋形态、促进免疫逃避以及协助支持 CagA 和 VacA 等重要毒力因子的功能[55]。CGT 也参与到干扰宿主细胞自噬流，促进 *H. pylori* 在宿主细胞内稳定存活[56]。研究通过活细胞成像以及共聚焦显微镜观察细胞吞噬运输过程发现，*H. pylori* 的 CGT 可干扰吞噬体运输，从而延缓巨噬细胞对其的内化以及抑制吞

噬体的成熟，从而促进 *H. pylori* 的胞内存活[53]。

2 幽门螺杆菌多重耐药性对临床诊断的挑战

2.1 菌株培养检测耐药

菌株培养的检测技术是 *H. pylori* 耐药性检测的金标准[9]，是指用琼脂稀释法(agar dilution method, ADM)或 Epsilometer 测试(E-test)等其他培养技术，定量确定在培养约 72 h 后杀死(杀菌活性)或抑制 *H. pylori* 生长(抑菌活性)的抗菌剂的最低浓度[57]。琼脂稀释法的准确性高，能够对多种抗生素进行敏感性检测[58]。E-test 操作简单、耗时较短，是临床中常用的一种替代方法[59]。然而，这 2 种方法都有较大的局限性，*H. pylori* 体外培养困难导致检测结果准确性不高，检测流程缺乏标准化，并且检测过程耗时长[59]。

2.2 PCR 检测基因耐药

H. pylori 的耐药性主要由相关基因小区域的特异性点突变导致，所以可以利用分子生物学方法检测 *H. pylori* 编码耐药性的特定基因突变，从而预测菌株抗生素敏感性。常用的检测技术有常规 PCR、实时荧光 PCR (real time PCR, RT-PCR)、数字 PCR (droplet digital PCR, ddPCR)、实时荧光定量聚合酶链反应(quantitative real-time PCR, qRT-PCR)等。PCR 技术可直接检测基因中的点突变，从而预测细菌对特定抗生素的耐药性[58]。本课题组研究了基于幽门螺杆菌 *cgt* 基因表达量测定活菌的方法，可检测 10 CFU/mL 的 *H. pylori*，特异性好且有效缩短了检测周期，为临床活菌检测和耐药测定提供了新方法[60]。

2.3 基因组测序检测耐药

DNA 测序技术能够同时分析幽门螺杆菌对 CLA 和 LEV 的耐药性[61-62]。其中新一代测序技术(next-generation sequencing, NGS)与 PCR 技术的基因耐药检测相比，突破了标本质量、成本和技术要求的限制，能够同时对数百万个 DNA 或 RNA 序列进行测序[63-64]。不仅如此，NGS 检测方法还能够提供更全面的细菌基因型视图，检测假阴性率会更低，具有在临床分离菌株中发现新型或罕见耐药机制的潜力[65-66]。然而，该技术在临床应用中仍然面临诸多挑战，包括临床表型与基因型一致性的验证不足、成本高、周期长以及临床医生对测序结果解读的理解程度有待提高，缺乏 *H. pylori* 耐药基因谱研究和耐药基因快速低成本检查方法已成为临床治疗的主要瓶颈。

3 *H. pylori* 多重耐药性对药物研发的挑战

Kuo 等[67]发现，*H. pylori* 的高耐药率使得常规的三联和四联疗法疗效显著降低，增加了患者的医疗成本。由于 *H. pylori* 感染人数高，不规范抗生素使用广泛，引起抗生素耐药菌株的增加，亟待寻找特异的靶向 *H. pylori* 的新抗菌药物。针对 *H. pylori* 多重耐药问题，研究者们正在积极探索多种新药开发策略，以应对抗生素耐药性的严峻挑战。例如：靶向 *cgt* 基因的 RNA 干扰技术、靶向 CGT 酶活性中心的抗体药物、微生态制剂、中药、小分子化合物(O-聚糖)等。

RNA 干扰(RNA interference, RNAi)技术可被用于减少基因的 mRNA 水平，进而阻断细菌的生长和繁殖。例如，5′ ureB-sRNA 通过促进转录终止的方式下调幽门螺杆菌 *ureAB* 基因的表达，减少脲酶的合成，进而调控幽门螺杆菌在不同 pH 环境下的生存[68]。Reza 等[69]的研究表明 siRNA 首先进入细胞并与 RNA 诱导的沉默复合体(RNA-induced silencing complex, RISC)结合，RISC 会将 siRNA 引导的向导链(guide strand)与目标 mRNA 结合；此时，RISC

中的 Ago2 (argonaute 2)蛋白会切割目标 mRNA 导致其降解，进而阻止 CagA 和 VacA 的蛋白质表达，阻止细菌的致病作用。此外，还可以开发特异性靶向 CGT 酶活性中心的抗体药物。这种抗体能够特异性识别并结合 *H. pylori* 的 CGT 酶，抑制其正常的代谢功能，最终导致细菌死亡。通过微生态制剂(如益生菌)的使用，如乳酸杆菌和双歧杆菌能够通过竞争性抑制 *H. pylori* 的黏附，分泌抗菌物质调节胃肠道微生态，从而有助于降低细菌数量和改善胃肠道炎症[69]。中药在抗幽门螺杆菌感染方面也展现出了巨大的潜力。Yoon 等[70]研究表明，含有甘草提取物的发酵牛奶能够减少 *H. pylori* 的密度，并改善胃肠道的炎症反应，Li 等[71]概述了这一迅速发展的领域。

小分子化合物如O-聚糖能够阻断其与宿主细胞的结合，进而抑制感染的发生和扩散[72]。这种策略在理论上能降低细菌对常规抗生素的依赖性，提供一种较为创新的治疗途径。Kawakubo 等[73]研究发现，深层胃黏膜分泌的物质 α1,4-连接的 N-乙酰葡萄糖胺(α1,4-GlcNAc)封端的 O-聚糖能竞争性抑制 CGT 活性，可能是阻止 *H. pylori* 在深层胃黏膜定植的重要因素，*H. pylori* 的感染与耐药都与 *cgt* 基因有关，本课题组于 2023 年提出 O-聚糖是靶向预防和治疗 *H. pylori* 的最理想的药物[72]，但其具体的体外抗胞内胞外感染的作用和机制亟待研究。此外针对 *cgt* 基因的 RNA 干扰开发的反义核酸药物或靶向针对 CGT 酶活性中心的单抗药物也是靶向防治的新策略。综上所述，当前幽门螺杆菌新药研发的方向如图 2 所示。

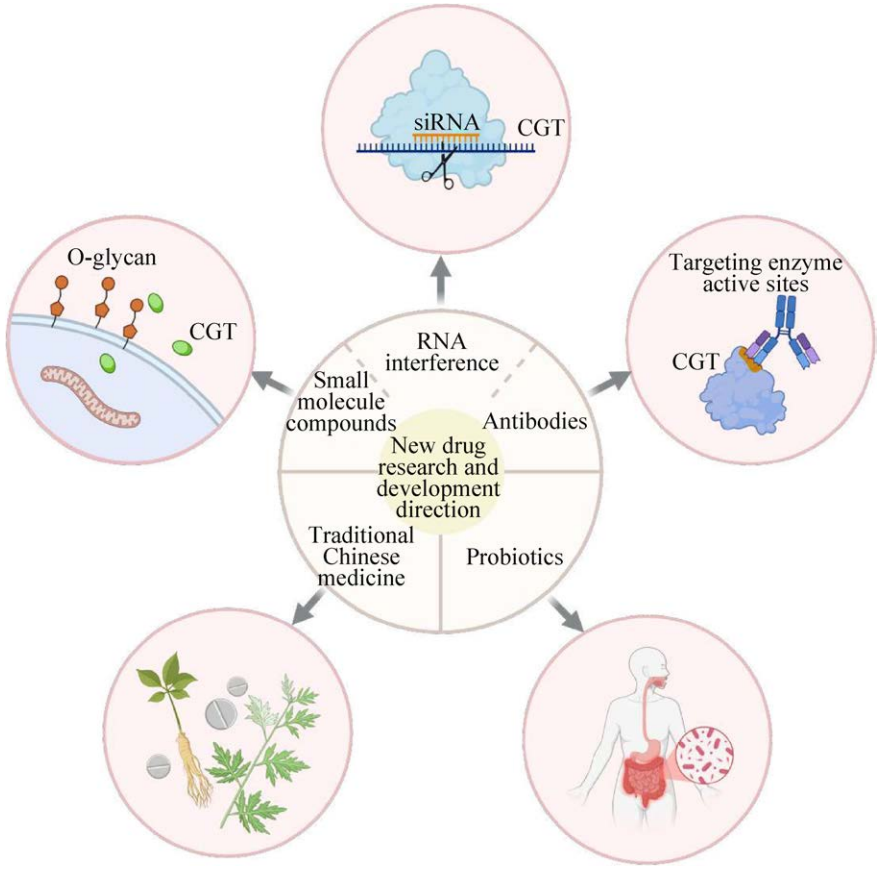

图 2　幽门螺杆菌新药研发的方向

Figure 2　Direction of research and development of new drugs for *Helicobacter pylori*.

4 总结与展望

H. pylori 感染在全球范围内发病率高并且感染人群广泛，常用的标准三联疗法(PPI、CLA和 AMX/MET)的治愈率已经下降至 80%以下[74]，而其复发率仍在上升。多重耐药问题已成为慢性胃病治疗失败及耐药菌株传播风险增加的一大严峻挑战。这一挑战尤其体现在临床诊断方法的改进、诊断标准的制定、耐药谱系的确认、新药研发的靶点筛选、精准靶向治疗药物的开发以及新型抗菌生物制剂的研制等方面。此外，社会对多重耐药 *H. pylori* 的认知以及耐药管理的重视程度也直接影响着 *H. pylori* 感染的防治效果。本文基于全球耐药相关文献和研究数据，系统回顾了 *H. pylori* 多重耐药性的全球流行趋势、发生机制及其对临床诊断和药物研发的挑战，同时提出了创新性的防治策略。研究人员要勇于担当、科学作为，遵循高福院士提出的“从理论到产品”的九层研发体系——想法、假说、实验、概念、论文、技术、样品、产品、商品，以此为指导框架，系统化地解决所面临的耐药问题[75]。倡导加强对 *H. pylori* 耐药性的监测和基因组学研究，确定耐药基因谱，开发快速、低成本的耐药性检测方法，以关键分子 *cgt* 基因或 CGT 酶活性为靶点开发新型药物。提倡在临床广泛开展分子诊断技术与个性化治疗策略的应用研究，有效地应对 *H. pylori* 多重耐药性带来的公共卫生挑战。

作者贡献声明

严茜雅：方案设计、初稿写作；郑璨璘：数据管理、方案设计、稿件润色修改；唐智慧：数据管理、提供材料；冯友军和王保宁：监督指导、稿件润色修改。

作者利益冲突公开声明

作者声明没有任何可能会影响本文所报告工作的已知经济利益或个人关系。

REFERENCES

[1] MARSHALL B, WARREN JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration[J]. The Lancet, 1984, 323(8390): 1311-1315.

[2] BOYANOVA L, HADZHIYSKI P, GERGOVA R, MARKOVSKA R. Evolution of *Helicobacter pylori* resistance to antibiotics: a topic of increasing concern[J]. Antibiotics, 2023, 12(2): 332.

[3] HU Y, ZHU Y, LU NH. Novel and effective therapeutic regimens for *Helicobacter pylori* in an era of increasing antibiotic resistance[J]. Frontiers in Cellular and Infection Microbiology, 2017, 7: 168.

[4] ANNIBALE B, CAPURSO G, DELLE FAVE G. Consequences of *Helicobacter pylori* infection on the absorption of micronutrients[J]. Digestive and Liver Disease, 2002, 34: S72-S77.

[5] MILLER AK, WILLIAMS SM. *Helicobacter pylori* infection causes both protective and deleterious effects in human health and disease[J]. Genes and Immunity, 2021, 22(4): 218-226.

[6] ROBINSON K, ATHERTON JC. The spectrum of*Helicobacter*-mediated diseases[J]. Annual Review of Pathology: Mechanisms of Disease, 2021, 16: 123-144.

[7] TACCONELLI E, CARRARA E, SAVOLDI A, HARBARTH S, MENDELSON M, MONNET DL, PULCINI C, KAHLMETER G, KLUYTMANS J, CARMELI Y, OUELLETTE M, OUTTERSON K, PATEL J, CAVALERI M, COX EM, HOUCHENS CR, GRAYSON ML, HANSEN P, SINGH N, THEURETZBACHER U, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis[J]. The Lancet Infectious Diseases, 2018, 18(3): 318-327.

[8] ZERBETTO de PALMA G, MENDIONDO N, WONAGA A, VIOLA L, IBARRA D, CAMPITELLI E, SALIM N, CORTI R, GOLDMAN C, CATALANO M. Occurrence of mutations in the antimicrobial target genes related to levofloxacin, clarithromycin, and amoxicillin resistance in *Helicobacter pylori* isolates from Buenos Aires City[J]. Microbial Drug Resistance, 2017, 23(3): 351-358.

[9] MALFERTHEINER P, MÉGRAUD F, O'MORAIN C, BELL D, BIANCHI PORRO G, DELTENRE M, FORMAN D, GASBARRINI G, JAUP B, MISIEWICZ JJ, PAJARES J, QUINA M, RAUWS E. Current European concepts in the management of *Helicobacter pylori* infection: the Maastricht Consensus Report. The European *Helicobacter Pylori* Study Group (EHPSG)[J]. European Journal of Gastroenterology & Hepatology, 1997, 9(1): 1-2.

[10] KATELARIS P, HUNT R, BAZZOLI F, COHEN H, FOCK KM, GEMILYAN M, MALFERTHEINER P, MÉGRAUD F, PISCOYA A, QUACH D, VAKIL N, VAZ COELHO LG, LeMAIR A, MELBERG J. *Helicobacter pylori* world gastroenterology organization global guideline[J]. Journal of Clinical Gastroenterology, 2023, 57(2): 111-126.

[11] HORIKI N, OMATA F, UEMURA M, SUZUKI S, ISHII N, IIZUKA Y, FUKUDA K, FUJITA Y, KATSURAHARA M, ITO T, CESAR GE, IMOTO I, TAKEI Y. Annual change of primary resistance to clarithromycin among *Helicobacter pylori* isolates

from 1996 through 2008 in Japan[J]. Helicobacter, 2009, 14(5): 86-90.
[12] SHIOTA S, REDDY R, ALSARRAJ A, EL-SERAG HB, GRAHAM DY. Antibiotic resistance of *Helicobacter pylori* among male United States veterans[J]. Clinical Gastroenterology and Hepatology, 2015, 13(9): 1616-1624.
[13] SAVOLDI A, CARRARA E, GRAHAM DY, CONTI M, TACCONELLI E. Prevalence of antibiotic resistance in *Helicobacter pylori*: a systematic review and meta-analysis in World Health Organization regions[J]. Gastroenterology, 2018, 155(5): 1372-1382.e17.
[14] 张菲菲, 王启, 李曙光, 王占伟, 梁馨月, 孟涵, 杨硕, 王辉. 幽门螺杆菌临床耐药性及其变化趋势: 北京大学人民医院 10 年数据分析[J]. 协和医学杂志, 2023, 14(5): 1017-1022.
ZHANG FF, WANG Q, LI SG, WANG ZW, LIANG XY, MENG H, YANG S, WANG H. Clinical resistance of *helicobacter pylori* and its trend: a 10-year data analysis at Peking University People's Hospital[J]. Peking Union Medical College Journal, 2023, 14(5): 1017-1022 (in Chinese).
[15] 张薇, 吴李培, 宣世海. 东台地区幽门螺杆菌多重耐药现状和相关基因突变的分析[J]. 实用预防医学, 2019, 26(3): 364-367.
ZHANG W, WU LP, XUAN SH. Analysis of multidrug resistance status and related gene mutations of *Helicobacter pylori* in the Dongtai region[J]. Practical Preventive Medicine, 2019, 26(3): 364-367 (in Chinese).
[16] 李晓华, 黄赞松, 黄衍强, 周喜汉, 吴明慧, 刘丽, 覃艳春, 黄干荣. 桂西地区幽门螺杆菌多重耐药现状和治疗方案分析[J]. 重庆医学, 2013, 42(14): 1578-1579, 1582.
LI XH, HUANG ZS, HUANG YQ, ZHOU XH, WU MH, LIU L, QIN YC, HUANG GR. Status quo of *Helicobacter pylori* multidrug resistance in west Guangxi area and analysis on treatment schemes[J]. Chongqing Medicine, 2013, 42(14): 1578-1579, 1582 (in Chinese).
[17] 王莉莉, 杨超, 董全江, 孙桂荣. 青岛地区幽门螺杆菌多重耐药现状和突变特征分析[J]. 国际检验医学杂志, 2015, 36(24): 3583-3585.
WANG LL, YANG C, DONG QJ, SUN GR. Prevalence andgenetic features of multi-drug resistant *Helicobacter pylori* strains from Qingdao[J]. International Journal of Laboratory Medicine, 2015, 36(24): 3583-3585 (in Chinese).
[18] PARK JY, SHIN TS, KIM JH, YOON HJ, KIM BJ, KIM JG. The prevalence of multidrug resistance of *Helicobacter pylori* and its impact on eradication in Korea from 2017 to 2019: A single-center study[J]. Antibiotics, 2020, 9(10): 646.
[19] BOLOR-ERDENE M, NAMDAG B, YAMAOKA Y, JAV S. Antibiotic resistance of *Helicobacter pylori* in Mongolia[J]. The Journal of Infection in Developing Countries, 2017, 11(11): 887-894.
[20] SUKRI A, HANAFIAH A, YUSOFF H, NIZAM NAS, NAMEYRRA Z, WONG Z, ALI RA. Multidrug-resistant *Helicobacter pylori* strains: A five-year surveillance study and its genome characteristics[J]. Antibiotics, 2022, 11(10): 1391.
[21] BOYANOVA L, HADZHIYSKI P, KANDILAROV N, MARKOVSKA R, MITOV I. Multidrug resistance in *Helicobacter pylori*: Current state and future directions[J]. Expert Review of Clinical Pharmacology, 2019, 12(9): 909-915.
[22] SUKRI A, LOPES BS, HANAFIAH A. The emergence of multidrug-resistant *Helicobacter pylori* in Southeast Asia: A systematic review on the trends and intervention strategies using antimicrobial peptides[J]. Antibiotics, 2021, 10(9): 1061.
[23] SANIEE P, HOSSEINI F, KADKHODAEI S, SIAVOSHI F, KHALILI-SAMANI S. *Helicobacter pylori* multidrug resistance due to misuse of antibiotics in Iran[J]. Arch Iran Med, 2018, 21(7): 283-288.
[24] LOPO I, LIBÂNIO D, PITA I, DINIS-RIBEIRO M, PIMENTEL-NUNES P. *Helicobacter pylori* antibiotic resistance in Portugal: Systematic review and meta-analysis[J]. Helicobacter, 2018, 23(4): e12493.
[25] FIORINI G, ZULLO A, SARACINO IM, PAVONI M, VAIRA D. Antibiotic resistance pattern of *Helicobacter pylori* strains isolated in Italy during 2010–2016[J]. Scandinavian Journal of Gastroenterology, 2018, 53(6): 661-664.
[26] BLUEMEL B, GOELZ H, GOLDMANN B, GRÜGER J, HAMEL H, LOLEY K, LUDOLPH T, MEYER J, MIEHLKE S, MOHR A, TÜFFERS K, USADEL H, WAGNER S, WENZEL H, WIEMER L, VORREITER J, EISELE B, HOFREUTER D, GLOCKER EO. Antimicrobial resistance of *Helicobacter pylori* in Germany, 2015 to 2018[J]. Clinical Microbiology and Infection, 2020, 26(2): 235-239.
[27] KHOURY J, GEFFEN Y, SHAUL R, SHOLY H, CHOWERS Y, SAADI T. Secondary antibiotic resistance of *Helicobacter pylori* isolates in Israeli children and adults[J]. Journal of Global Antimicrobial Resistance, 2017, 10: 182-185.
[28] PARRA-SEPÚLVEDA C, MERINO JS, SÁEZ-CARRILLO K, GONZÁLEZ C, GARCÍA-CANCINO A. Antibiotic resistance surveillance of *Helicobacter pylori* at the Biobío region (Chile) in a decade[J]. Arquivos de Gastroenterologia, 2019, 56(4): 361-366.
[29] MEGRAUD F, BRUYNDONCKX R, COENEN S, WITTKOP L, HUANG TD, HOEBEKE M, BÉNÉJAT L, LEHOURS P, GOOSSENS H, GLUPCZYNSKI Y, European *Helicobacter pylori* antimicrobial susceptibility testing working group. *Helicobacter pylori* resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community[J]. Gut, 2021, 70(10): 1815-1822.
[30] POOLE K. Efflux-mediated multiresistance in gram-negative bacteria[J]. Clinical Microbiology and Infection, 2004, 10(1): 12-26.
[31] TSHIBANGU-KABAMBA E, YAMAOKA Y. *Helicobacter pylori* infection and antibiotic resistance: from biology to clinical implications[J]. Nature Reviews Gastroenterology & Hepatology, 2021, 18: 613-629.
[32] GONG YH, YUAN Y. Resistance mechanisms of *Helicobacter pylori* and its dual target precise therapy[J]. Critical Reviews in Microbiology, 2018, 44(3): 371-392.
[33] TRAN TT, NGUYEN AT, QUACH DT, PHAM DT, CAO NM, NGUYEN UT, DANG AN, TRAN MA, QUACH LH, TRAN KT, LE NQ, UNG VV, VO MN, NGUYEN DT, NGO KD, TRAN TL, NGUYEN VT.

Emergence of amoxicillin resistance and identification of novel mutations of the pbp1A gene in *Helicobacter pylori* in Vietnam[J]. BMC Microbiology, 2022, 22(1): 41.
[34] TSENG YS, WU DC, CHANG CY, KUO CH, YANG YC, JAN CM, SU YC, KUO FC, CHANG LL. Amoxicillin resistance with beta-lactamase production in *Helicobacter pylori*[J]. European Journal of Clinical Investigation, 2009, 39(9): 807-812.
[35] QURESHI NN, GALLAHER B, SCHILLER NL. Evolution of amoxicillin resistance of *Helicobacter pylori in vitro*: characterization of resistance mechanisms[J]. Microbial Drug Resistance, 2014, 20(6): 509-516.
[36] RIMBARA E, MORI S, KIM H, SUZUKI M, SHIBAYAMA K. Mutations in genes encoding penicillin-binding proteins and efflux pumps play a role in β-lactam resistance in *Helicobacter cinaedi*[J]. Antimicrobial Agents and Chemotherapy, 2018, 62(2): e02036-17.
[37] PUAH SM, GOH KL, NG HK, CHUA KH. Current status of *Helicobacter pylori* resistance to Clarithromycin and Levofloxacin in Malaysia-findings from a molecular based study[J]. PeerJ, 2021, 9: e11518.
[38] LI YX, LV TS, HE CC, WANG HY, CRAM DS, ZHOU LF, ZHANG J, JIANG WQ. Evaluation of multiplex ARMS-PCR for detection of *Helicobacter pylori* mutations conferring resistance to clarithromycin and levofloxacin[J]. Gut Pathogens, 2020, 12: 35.
[39] BINH TT, SHIOTA S, SUZUKI R, MATSUDA M, TRANG TTH, KWON DH, IWATANI S, YAMAOKA Y. Discovery of novel mutations for clarithromycin resistance in *Helicobacter pylori* by using next-generation sequencing[J]. Journal of Antimicrobial Chemotherapy, 2014, 69(7): 1796-1803.
[40] ZAMANI M, RAHBAR A, SHOKRI-SHIRVANI J. Resistance of *Helicobacter pylori* to furazolidone and levofloxacin: a viewpoint[J]. World Journal of Gastroenterology, 2017, 23(37): 6920-6922.
[41] GARCIA M, RAYMOND J, GARNIER M, CREMNITER J, BURUCOA C. Distribution of spontaneous gyrA mutations in 97 fluoroquinolone-resistant *Helicobacter pylori* isolates collected in France[J]. Antimicrobial Agents and Chemotherapy, 2012, 56(1): 550-551.
[42] ZHANG SZ, WANG XY, WISE MJ, HE YS, CHEN HT, LIU AJ, HUANG HY, YOUNG S, TAY CY, MARSHALL BJ, LI XH, CHUA EG. Mutations of *Helicobacter pylori* RdxA are mainly related to the phylogenetic origin of the strain and not to metronidazole resistance[J]. Journal of Antimicrobial Chemotherapy, 2020, 75(11): 3152-3155.
[43] NISHIZAWA T, SUZUKI H. Mechanisms of *Helicobacter pylori* antibiotic resistance and molecular testing[J]. Frontiers in Molecular Biosciences, 2014, 1: 19.
[44] WU JY, KIM JJ, REDDY R, WANG WM, GRAHAM DY, KWON DH. Tetracycline-resistant clinical *Helicobacter pylori* isolates with and without mutations in 16S rRNA-encoding genes[J]. Antimicrobial Agents and Chemotherapy, 2005, 49(2): 578-583.
[45] TRIEBER CA, TAYLOR DE. Mutations in the 16S rRNA genes of *Helicobacter pylori* mediate resistance to tetracycline[J]. Journal of Bacteriology, 2002, 184(8): 2131-2140.
[46] 刘成程, 胡小芳, 冯友军. 细菌耐药: 生化机制与应对策略[J]. 生物技术通报, 2022, 38(9): 4-16.
LIU CC, HU XF, FENG YJ. Antimicrobial resistance: biochemical mechanisms and countermeasures[J]. Biotechnology Bulletin, 2022, 38(9): 4-16 (in Chinese).
[47] LIU ZQ, ZHENG PY, YANG PC. Efflux pump gene hefA of *Helicobacter pylori* plays an important role in multidrug resistance[J]. World Journal of Gastroenterology, 2008, 14(33): 5217-5222.
[48] CAI YY, WANG CX, CHEN ZH, XU ZZ, LI HJ, LI WJ, SUN YD. Transporters HP0939, HP0497, and HP0471 participate in intrinsic multidrug resistance and biofilm formation in *Helicobacter pylori* by enhancing drug efflux[J]. Helicobacter, 2020, 25(4): e12715.
[49] YONEZAWA H, OSAKI T, HOJO F, KAMIYA S. Effect of *Helicobacter pylori* biofilm formation on susceptibility to amoxicillin, metronidazole and clarithromycin[J]. Microbial Pathogenesis, 2019, 132: 100-108.
[50] 唐智慧, 符立发, 刘人捷, 陈昱作, 别明江, 王保宁. 幽门螺杆菌胞内感染机制与临床思考[J]. 四川大学学报(医学版), 2023, 54(6): 1300-1305.
TANG ZH, FU LF, LIU RJ, CHEN YZ, BIE MJ, WANG BN. Mechanisms of *Helicobacter pylori* intracellular infection and reflections concerning clinical practice[J]. Journal of Sichuan University (Medical Sciences), 2023, 54(6): 1300-1305 (in Chinese).
[51] QARIA MA, KUMAR N, HUSSAIN A, QUMAR S, DODDAM SN, SEPE LP, AHMED N. Roles of cholesteryl-α-glucoside transferase and cholesteryl glucosides in maintenance of *Helicobacter pylori* morphology, cell wall integrity, and resistance to antibiotics[J]. mBio, 2018, 9(6): e01523-18.
[52] MOREY P, PFANNKUCH L, PANG E, BOCCELLATO F, SIGAL M, IMAI-MATSUSHIMA A, DYER V, KOCH M, MOLLENKOPF HJ, SCHLAERMANN P, MEYER TF. *Helicobacter pylori* depletes cholesterol in gastric glands to prevent interferon gamma signaling and escape the inflammatory response[J]. Gastroenterology, 2018, 154(5): 1391-1404.e9.
[53] DU SY, WANG HJ, CHENG HH, CHEN SD, WANG LH, WANG WC. Cholesterol glucosylation by *Helicobacter pylori* delays internalization and arrests phagosome maturation in macrophages[J]. Journal of Microbiology, Immunology and Infection, 2016, 49(5): 636-645.
[54] FAIT A, ANDERSSON DI, INGMER H. Evolutionary history of *Staphylococcus aureus* influences antibiotic resistance evolution[J]. Current Biology, 2023, 33(16): 3389-3397.e5.
[55] QARIA MA, QUMAR S, SEPE LP, AHMED N. Cholesterol glucosylation-based survival strategy in *Helicobacter pylori*[J]. Helicobacter, 2021, 26(2): e12777.
[56] MUTHUSAMY S, JAN HM, HSIEH MY, MONDAL S, LIU WC, KO YA, YANG WY, MONG KT, CHEN GC, LIN CH. Enhanced enzymatic production of cholesteryl 6′-acylglucoside impairs lysosomal degradation for the intracellular survival of *Helicobacter pylori*[J]. Journal of Biomedical Science, 2021, 28(1): 72.
[57] LI H, SHEN YL, SONG XN, TANG XQ, HU RW,

MARSHALL BJ, TANG H, BENGHEZAL M. Need for standardization and harmonization of *Helicobacter pylori* antimicrobial susceptibility testing[J]. Helicobacter, 2022, 27(2): e12873.
[58] JEARTH V, RATH MM, CHATTERJEE A, KALE A, PANIGRAHI MK. Drug-resistant *Helicobacter pylori*: diagnosis and evidence-based approach[J]. Diagnostics, 2023, 13(18): 2944.
[59] MIFTAHUSSURUR M, FAUZIA KA, NUSI IA, SETIAWAN PB, SYAM AF, WASKITO LA, DOOHAN D, RATNASARI N, KHOMSAN A, ADNYANA IK, AKADA J, YAMAOKA Y. E-test versus agar dilution for antibiotic susceptibility testing of *Helicobacter pylori*: a comparison study[J]. BMC Research Notes, 2020, 13(1): 22.
[60] 唐智慧, 符立发, 张焱荣, 周博彦, 冯天勤, 杨文娟, 梁鸽, 严茜雅, 郑璨璘, 别明江, 王保宁. 幽门螺杆菌 cgt 基因表达量测定活菌的方法建立及应用研究[J]. 四川大学学报(医学版), 2024, 55(5): 1316-1321.
TANG ZH, FU LF, ZHANG YR, ZHOU BY, FENG TQ, YANG WJ, LIANG G, YAN QY, ZHENG CL, BIE MJ, WANG BN. Viable bacteria assay of *Helicobacter pylori* by RT-qPCR measurement of cgt gene expression levels: establishment and application of a new method[J]. Journal of Sichuan University (Medical Sciences), 2024, 55(5): 1316-1321 (in Chinese).
[61] 刘人捷, 陈昱作, 唐智慧, 符立发, 杨露, 王保宁. 四种幽门螺杆菌检测方法的灵敏度比较实验[J]. 四川大学学报(医学版), 2022, 53(3): 421-425.
LIU RJ, CHEN YZ, TANG ZH, FU LF, YANG L, WANG BN. Sensitivity comparison experiment of four testing methods for *Helicobacter pylori*[J]. Journal of Sichuan University (Medical Sciences), 2022, 53(3): 421-425 (in Chinese).
[62] MEDAKINA I, TSAPKOVA L, POLYAKOVA V, NIKOLAEV S, YANOVA T, DEKHNICH N, KHATKOV I, BORDIN D, BODUNOVA N. *Helicobacter pylori* antibiotic resistance: molecular basis and diagnostic methods[J]. International Journal of Molecular Sciences, 2023, 24(11): 9433.
[63] SARUULJAVKHLAN B, YAMAOKA Y. Benefits of a molecular-based method for the detection of clarithromycin-resistant *Helicobacter pylori*[J]. Gut and Liver, 2021, 15(4): 487-489.
[64] BOUNAADJA L, ALBERT D, CHÉNAIS B, HÉNAULT S, ZYGMUNT MS, POLIAK S, GARIN-BASTUJI B. Real-time *PCR* for identification of *Brucella* spp.: a comparative study of IS711 bcsp31 and per target genes[J]. Veterinary Microbiology, 2009, 137(1/2): 156-164.
[65] ZHONG YM, XU F, WU JH, SCHUBERT J, LI MM. Application of next generation sequencing in laboratory medicine[J]. Annals of Laboratory Medicine, 2021, 41(1): 25-43.
[66] MALJKOVIC BERRY I, MELENDREZ MC, BISHOP-LILLY KA, RUTVISUTTINUNT W, POLLETT S, TALUNDZIC E, MORTON L, JARMAN RG. Next generation sequencing and bioinformatics methodologies for infectious disease research and public health: approaches, applications, and considerations for development of laboratory capacity[J]. The Journal of Infectious Diseases, 2020, 221(Suppl 3): S292-S307.
[67] KUO CJ, LEE CH, CHANG ML, LIN CY, LIN WR, SU MY, CHIU CH, TSENG CN, WU YS, CHIU CT, LAI CH. Multidrug resistance: The clinical dilemma of refractory *Helicobacter pylori* infection[J]. Journal of Microbiology, Immunology and Infection, 2021, 54(6): 1184-1187.
[68] WEN Y, FENG J, SACHS G. *Helicobacter pylori* 5′ureB-sRNA, a *Cis*-encoded antisense small RNA, negatively regulates ureAB expression by transcription termination[J]. Journal of Bacteriology, 2013, 195(3): 444-452.
[69] REZA MN, MAHMUD S, FERDOUS N, AHAMMAD I, HOSSAIN MU, AL AMIN M, MOHIUDDIN AM. Gene silencing of *Helicobacter pylori* through newly designed siRNA convenes the treatment of gastric cancer[J]. Cancer Medicine, 2023, 12(24): 22407-22419.
[70] YOON JY, CHA JM, HONG SS, KIM HK, KWAK MS, JEON JW, SHIN HP. Fermented milk containing *Lactobacillus paracasei* and *Glycyrrhiza glabra* has a beneficial effect in patients with *Helicobacter pylori* infection: a randomized, double-blind, placebo-controlled study[J]. Medicine, 2019, 98(35): e16601.
[71] LI YL, LI XY, TAN ZJ. An overview of traditional Chinese medicine therapy for *Helicobacter pylori*-related gastritis[J]. Helicobacter, 2021, 26(3): e12799.
[72] CHEN YZ, TANG ZH, FU LF, LIU RJ, YANG L, WANG BN. Inhibitory and injury-protection effects of O-glycan on gastric epithelial cells infected with *Helicobacter pylori*[J]. Infection and Immunity, 2022, 90(10): e0039322.
[73] KAWAKUBO M, ITO Y, OKIMURA Y, KOBAYASHI M, SAKURA K, KASAMA S, FUKUDA MN, FUKUDA M, KATSUYAMA T, NAKAYAMA J. Natural antibiotic function of a human gastric mucin against *Helicobacter pylori* infection[J]. Science, 2004, 305(5686): 1003-1006.
[74] GODAVARTHY PK, PULI C. From antibiotic resistance to antibiotic renaissance: a new era in *Helicobacter pylori* treatment[J]. Cureus, 2023, 15(3): e36041.
[75] 高福. 国家人勇担国家责, 积极推动中国生物经济与生物产业发展[J]. 生物工程学报, 2022, 38(11): 4012-4018.
GAO F. Active promotion of bio-industry technology development in China[J]. Chinese Journal of Biotechnology, 2022, 38(11): 4012-4018 (in Chinese).