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携手探索创新求实

第十六届全国幽门螺杆菌及消化疾病诊治临床论坛
第五届全国幽门螺杆菌与胃肠生态中西医整合高峰论坛
暨第六届湖南幽门螺杆菌相关疾病及消化疾病诊治论坛

北京医学会
中国幽门螺杆菌信息中心
北京大学第一医院
中华医学会《中华医学杂志》
湖南医学会内科学会幽门螺杆菌学组
中南大学湘雅医院
中国医促会中西医结合消化分会
全国幽门螺杆菌防治联盟

康哲药业 CHINA MEDICAL SYSTEM 深圳市康哲药业有限公司

JUMPCAN 济川药业 济川药业集团有限公司

大爱高寿网(diagoso.net)

湖南-长沙

2021.12.10-12

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《第十六届全国HP及消化疾病诊治临床论坛》感言
--衷心感谢支持论坛的所有朋友们!

胡伏莲 2021-10-19

因为阳光 花儿才会绽放
因为雨露 原野才会披上绿装
因为春风 才会送来鸟语花香
因为播种 才会有收获

今年是一个值得纪念的一年
今年是《全国HP临床论坛》创立16周年
今年是我国首部《整合胃生态学》正式出版发行的一年
让我们共同来庆祝大家的劳动成果

HP的发现
是医学史上的一件大事
是对消化性溃疡的一场革命
是对某些临床疾病重新认识的里程碑
是临床医生最关注的热点课题
《HP论坛》是我们携手合作研究的公众平台

我国是HP高感染率国家
我国是对HP研究高度重视的国家
16年前大家一起创立了《全国HP及消化疾病诊治临床论坛》
16年来大家努力不断
每年一次的论坛
来自全国各地的HP研究者的热情与执着在这里汇聚
对HP研究从认识-实践-到再认识
每年一次的论坛
来自HP研究的智慧与理性在这里碰撞
一系列有关HP的著作在这里诞生并与大家见面
一系列优秀论文在这里交流和发表
每年一次的论坛
来自社会、企业、学会、专家和领导的关爱在这里体现与表达
每年一次的论坛
来自全国各地的权威和专家在这里交流与倾听
每年一次的论坛
来自不同学科的专家和学者对HP的诊断和治疗达成了共识

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胡伏莲 2021-10-19

...接上页

《HP论坛》是历届年鉴，记載了消化精英丰功伟绩;
《HP论坛》是美丽画卷，展示了历届专家医学精彩;
《HP论坛》是医学智库，汇聚了专家和学者累累硕果;
《HP论坛》是北京医学会的奉献，体现了学会领导高度重视与关注;
《HP论坛》是时间通道，让我们看到过去，呈现现在，展望未来。

今天的成就来自于大家的支持
今天的成果饱含大家的辛劳
千言万语难表感激之情
千歌万曲唱不完彼此的友情与辛劳
相遇相知是缘份 志同道合是基石
携手 探索 创新 求实是我们论坛的宗旨

HP研究并未结束
需要研究的问题还很多！很多！
前进之路并非平坦 道路依旧崎岖
乌云可能密布 抑或狂风暴雨
让我们团结一致勇往直前！

今天我们相聚一堂
今天是一个分享快乐和成果的日子
我们的朋友来自五湖四海
我们的朋友来自全国各地
我们在这里尽情畅谈共同的理想与愿望
我们在这里相聚是彼此的荣幸和欢乐

啊！朋友啊！朋友！
不管你来自何方，让我们欢聚一堂
朋友啊！朋友！
不管你来自何方， 请把美酒来品尝
让我们汇入这学术的海洋
让我们享受这幸福的时光

第十六届全国幽门螺杆菌及消化疾病诊治临床论坛
第五届全国幽门螺杆菌与胃肠生态中西医整合高峰论坛
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由北京医学会、中国幽门螺杆菌信息中心(www.hpylori.cn)主办；由中华医学会《中华医学杂志》学术支持；由北京大学第一医院；湖南医学会内科学会幽门螺杆菌学组；中南大学湘雅医院；中国医促会中西医结合消化分会及“全国幽门螺杆菌防治联盟”共同举办的《第十六届全国幽门螺杆菌及消化疾病诊治临床论坛》、《第五届全国幽门螺杆菌与胃肠生态中西医整合高峰论坛》暨《第六届湖南幽门螺杆菌相关疾病及消化疾病诊治论坛》于2021年12月10-12日在长沙圣爵菲斯大酒店隆重举行。

本次论坛重点为以下几方面：1.幽门螺杆菌与消化疾病研究前沿；2.胃肠生态与人体健康；3.继续跟进《幽门螺杆菌治疗新路径》以及进一步验证和落实《全国中西医整合治疗幽门螺杆菌相关病-证共识》；4.青年优秀论文演讲赛和典型病例分享。论坛将以主题报告和青年分论坛形式进行。本次论坛将积极推荐优秀论文至《中华医学杂志》等相关杂志，经评审合格者可以发表。真诚欢迎全国消化界同道，中西医专家及幽门螺杆菌学者共同参与，分享和交流。

扫码直播：

第十六 HP 论坛 2021 年 11 月 13 日（周六上午）				
时间	**时长（分）**	**内容**	**讲者**	**主持人**
8:20	40	开幕式	张桂英 胡伏莲 张万岱 朱建华 张欣 刘新民 封国生	刘建湘 徐美华
9:00	15	我国首部《整合胃生态学》新著出版发布仪式	兰南 樊代明	张声生
9:15	15	中国健康促进基金会《幽门螺杆菌相关疾病防治公益项目》专家委员会成立仪式	常映明	苏迪
专题：消化疾病研究进展及整合医学				
9:30	35	整合消化病学进展	樊代明	张澍田 韩英 房殿春
10:05	20	胃食管反流与幽门螺杆菌	段丽萍	
10:25	20	PPI 与肠道微生态	唐承薇	
10:45	15	茶歇		
专题：幽门螺杆菌及相关疾病诊治				
11:00	20	根除幽门螺杆菌方案的变迁	张振玉	胡伏莲 刘小伟 吕相征
11:20	20	幽门螺杆菌的规范诊治	张桂英	
11:40	20	如何撰写论文	马军	
12:00	60	**午餐 +《整合胃生态学》新书抽奖活动**		杨桂彬 刘芳勋

第十六 HP 论坛 2021 年 11 月 13 日（周六下午）				
专题：“幽门螺杆菌治疗新路径”进展				
13:00	15	幽门螺杆菌相关疾病中医分型	张声生	邹多武
13:15	15	幽门螺杆菌中药治疗进展	张学智	陆红
13:30	25	核力卫星会	袁杰力	郑鹏远
13:55	15	幽门螺杆菌诊断方面进展及问题	张建中	吕宾
14:10	15	幽门螺杆菌的精准诊断	郜恒骏	王化虹
14:25	15	幽门螺杆菌感染诊断方法的评价与选择	王蔚虹	盛剑秋
14:40	15	慢性萎缩性胃炎的全病程管理	徐美华	张国新
14:55	15	**茶歇**		
15:10	15	MUC17 在 HP 感染相关胃癌中的表观遗传调控作用	吕有勇	
15:25	15	幽门螺杆菌感染与胃肠动力	刘建湘	崔梅花
15:40	15	幽门螺杆菌感染在动脉粥样硬化形成中的作用与机制	徐灿霞	田德安
15:55	25	甘海胃康研究进展	杨桂彬 杜奕奇	胡伏莲
16:20	25	幽门螺杆菌株分型研究进展	兰春慧	李建生
16:45	25	乳铁蛋白研究进展	董锦沛	吕涤非
17:10	10	蒲地蓝对幽门螺杆菌抑制作用的体外研究	成虹	冯桂建
17:20	10	胃铋镁对幽门螺杆菌抑制作用的实验研究	牟方宏	董欣红
17:30	10	卵黄抗体在幽门螺杆菌感染治疗中应用初探	徐灿霞	张桂英
17:40	140	**大会自助晚餐**		
20:00	60	工作会： 1. 全国幽门螺杆菌防治联盟专家会 2. 《整合胃生态学》作者合影总结会 3. 中国健康促进基金项目启动会		

第十六 HP 论坛 2021 年 11 月 14 日（周日上午）				
时间	**时长（分）**	**内容**	**讲者**	**主持人**
专题：消化疾病研究前沿及胃肠生态				
8:30	20	抗栓药物诱导消化道损伤与 HP 感染	王江滨	李岩 姜葵 兰春慧
8:50	20	益生菌在幽门螺杆菌根除中的治疗作用（在线）	陈烨	
9:10	20	整合医学之 MDT-to-HIM	杨志平	
9:30	25	幽门螺杆菌与胃肠微生态	王刚石	袁耀宗
9:55	25	碳十三呼气试验与活检胃组织尿素酶试验结合组织培养结果的对照试验	潘杰	张建中
10:20	15	茶歇		
专题：新睿论文				
10:35	10	多中心临床观察铝碳酸镁四联与铋剂四联根除幽门螺杆菌的疗效及安全性	贾燕	高文 汪春莲 杨铭
10:45	10	VacA 重组蛋白对 TRAF14-1BBNF-κB 通路活化及胃上皮细胞增殖与凋亡的影响	袁玲芝	
10:55	10	幽门螺杆菌耐药现状分析	吴聃	
11:05	10	铋剂四联 10 天疗法联合酪酸梭菌-聚普瑞锌治疗幽门螺旋杆菌感染的疗效分析	王烁	王学红 廖江涛 廖爱军 .
11:15	10	依从性良好幽门螺杆菌感染患者根除失败的危险因素	罗举	
11:25	10	无症状幽门螺杆菌感染典型“鸡皮样胃炎”1 例诊治体会	伍丽	
11:35	10	不同菌型 HP 与胃部疾病的相关性研究	赵文芳	申月明 宋丰前
11:45	10	Efficacy of bismuth-based quadruple therapy for eradication	周晶晶	
11:55	10	布拉氏酵母辅助治疗幽门螺杆菌感染的随机对照研究	屈鹏	王芬 王蔚虹
12:05	10	益君康辅助用于一例多次 HP 根除失败患者的思考	董昀凡	
12:15	10	论文颁奖仪式（领导+专家）		
12:25	10	闭幕式	胡伏莲	张桂英 成虹
12:35	120	**午餐 +《整合胃生态学》新书抽奖活动**		纪开宇 滕贵根

《第十六届全国幽门螺杆菌及消化疾病诊治临床论坛》

《第五届全国幽门螺杆菌与胃肠生态中西医整合高峰论坛》

暨

《第六届湖南幽门螺杆菌相关疾病及消化疾病诊治论坛》

名誉主席：樊代明

大会主席：胡伏莲 张桂英

执行主席：刘建湘 徐美华

共同主席: 袁耀宗 张澍田 李建生 唐旭东 张声生 段丽萍 唐承薇 韩英 房殿春 吕相征 王化虹 袁杰力

特约嘉宾 ：封国生 刘新民 兰南 吕相征 马军 常映明 苏迪 朱建华

大会秘书长: 成虹 徐灿霞 杨桂彬 高文 严璐

学术委员会秘书长: 王蔚虹 王芬

VIP 专家(拼音顺序): 陈烨 崔梅花 董蕾 董欣红 杜奕奇 冯桂建 郜恆骏 纪开宇 贾燕 姜葵 兰春慧 李岩 廖爱军 廖江涛 刘小伟 陆红 吕宾 吕有勇 牟方宏 申月明 盛剑秋 师伟 田德安 汪春莲 王刚石 王江滨 王学红 杨铭 杨志平 张国新 张学智 张振玉 郑鹏远 邹多武 张建中

秘书组: 牟方宏 董欣虹 刘芳勋 滕贵根 黄煌 刘晓明 董锦沛 马继征

医疗媒体:《中华医学杂志》:吕相征 周阳

《胃肠病学和肝病学杂志》：李建生

《胃肠病学和肝病学杂志》：马军

《人民卫生出版社》：兰南 孙瑞泽

《整合胃生态学》序

樊代明 中国工程院院士、副院长

以人体某一器官写医学专著，通常先写该器官的结构，再写功能，再写该器官结构和功能发生的变化或异常，即所致的相应疾病及诊治和预防。但是这本《整合胃生态学》主要不是写胃的结构和功能，也不写有结构和功能变化所致的疾病，而是专写胃腔内存在的微生态状况及其异常所致的疾病。目前，医学界专写肠道、呼吸道、泌尿生殖道、皮肤，甚至外耳道等器官微生态的专著不少，但写胃微生态的专著却不多，我印象这可能是第一本。因为长期以来认为，胃处于强酸状态，一般细菌是难以生存或生长的。

高度全面重视胃微生态是从上世纪 80 年代开始的，因为 J. Robin Warren 和 Barry J. Marshall 在研究中发现了幽门螺杆菌（Helicobacter pylori，H.pylori）及其在胃病中作用，后来因此获得了诺贝尔生理或医学奖。从那以后，H.pylori 逐渐成了细菌的明星、研究 H.pylori 的人成了名人、生产抗 H.pylori 药品的厂商成了名商，不过还有很多事情没说明白。比如 H.pylori 的疫苗至今尚不理想，于是相关疾病的预防还成问题；又如，H.pylori 抗药性致使三联、四联用药都难获理想效果；再如 H.pylori 与胃癌的关系事实上并无定论。

WHO 把 H.pylori 定义为胃癌的第一致癌因素，可有胃癌无 H.pylori，有 H.pylori 无胃癌的临床案例比比皆是。更重要的是，H.pylori 与胃内其他微生态之间的关系，胃微生态与全身生理状态，特别是其与全身各系统疾病之间的关系，都需要研究，因为这些问题一个套一个，一环扣一环，剪不断，理还乱，动一发而及全局。所以需要多角度、全因素考虑的整合医学研究。怎样解决这样的问题，急需整合医学研究。整合医学是整体整合医学（Holistic Integrative Medicine, HIM）的缩写。整合医学是从人的整体出发，将医学各领域最先进的理论知识和临床各专科最有效的实践经验分别加以有机整合，并根据社会、环境、心理的改变进行修正、调整，使之成为更加符合、更加适合人体健康和疾病诊疗预防的新的医学知识体系。《整合胃生态学》正是基于这样的认识论和方法学写成的，所以在“胃生态学”之前加了“整合”二字。

胡伏莲教授长期从事 H.pylori 的研究，她作为大会主席已先后举办了 13 届全国性 H.pylori 相关学术大会，是我国 H.pylori 基础研究和临床实践的重要贡献者。她组织全国的相关学者编写的这本《整合胃生态学》，立意新颖、内容丰富、思维深邃、视野广阔。既有基础研究中的最新成果，又有临床实践中的丰富经验，是一本非常重要、非常有用的专著，我有幸先睹为快，乐意推荐给相关学者。

《整合胃生态学》概述

北京航天中心医院 杨桂彬

北京大学第一医院 胡伏莲

一、胃内微环境

二、幽门螺杆菌

三、非幽门螺杆菌胃微生物群

四、幽门螺杆菌与其他胃微生物的关系

五、胃微生态与临床疾病的关系

（一）胃生态与慢性胃炎和消化性溃疡病

（二）胃生态与胃癌

（三）胃生态与其他上胃肠外疾病

六、小结

基于胃内强酸，曾一直被认为是一种无菌器官，1982年幽门螺杆菌（Helicobacter pylori，下称 H. pylori）的发现颠覆了这个传统的消化病理学的观点。而且有关微生态的研究方法取得很大进展，

过去依赖于细菌培养，现在的发包括温度梯度凝胶电泳、新一代测序技术、代谢组学和蛋白质组学技术等。这些技术可以更广泛地描述胃内微生物群落的结构和功能，极大地促进了对胃微生态的了解。*H. pylori* 不再被认为是胃中唯一的微生物，胃内还有很多其他微生物菌种，并发挥着重要作用。这些细菌可能同样与消化性溃疡、胃癌等胃十二指肠疾病有密切的关系，只有更好的了解胃微生物群的结构、功能，及其与胃肠道的相互作用，才能更全面地理解胃病的发病机制。

一、胃内微环境

胃的独特的解剖学、组织学及生理学特征，使得胃内微生态的组成与消化道的其他部分存在巨大的差异。强酸环境、胆汁反流、黏液厚度和胃蠕动等多种因素协同作用使得胃内形成一个强烈的抗菌环境。直到 1982 年 H. pylori 的发现才终结了传统的胃内无菌观念。

饮食习惯以及药物，也是胃生态组成的重要影响因素，有关饮食对肠道微生物群结构的影响研究较多，而对胃微生物多样性的影响知之甚少。有研究发现功能性消化不良患者胃内微生物群存在显著的失衡，用酸奶治疗可以纠正胃生态失衡，并且缓解消化不良的症状。

质子泵抑制剂（PPI）是影响胃微生物多样性一个重要因素，PPI 治疗会导致胃 pH 升高而便于微生物群落定植于胃环境中。有荟萃分析发现抑酸药物与胃癌风险增加有关，这可能与抑酸药物改变了胃生态有关。抗生素可以杀死胃生态中的细菌，从而改变正常的胃生态。有研究表明抗生素减少胃内细菌，但对真菌生物多样性无明显影响，这为保护胃内健康微生物组提供了新的方向。

二、幽门螺杆菌

当感染 H. pylori 时，H. pylori 成为胃生态中相对丰度最高的细菌。H. pylori 的发现改变了长期以来胃内无菌的传统观点，并提高了人们对微生物群落在恶劣的酸性环境中如何存活的理解。H. pylori 依靠鞭毛运动，产生的黏附因子、尿素酶和氨有助于细菌在不利的酸性环境中渗透、定殖和存活。H. pylori 的这些生物学的特征，可以使其定植于胃黏膜上皮，并产生致病作用。一旦定植，就会产生复杂的炎症反应，损伤胃黏膜，并可能导致相关的疾病。

H. pylori 的另一个重要特征是其巨大的遗传多样性，这源于 H. pylori 自身的高突变率及其与宿主不断交换遗传物质的特性。从世界不同地点分离出的不同菌株表明 H. pylori 在人类的整个历史进程中与人类共同进化。细菌、宿主和环境之间的相互作用会导致不同的临床结局，可能产生致病或保护作用。

三、非幽门螺杆菌胃微生物群

H. pylori 曾被认为是唯一能够在恶劣的胃环境中生存的生物，近年研究表明还有很多其他的微生物群落也存在于胃和十二指肠中。胃内微生物密度约为 102 至 104 CFU/mL，其胃内 pH、食物、药物，等因素都会影响胃内细菌密度。胃腔中的 pH 值中位数为 1.4，胃内的微生物密度显著低于结肠的 1010 至 1012CFU/mL。

胃液培养和黏膜活检是传统的研究胃内微生物的方法，由于大部分细菌无法培养[，这些技术低估了胃内细菌的生物多样性。目前已经开发了如全基因组测序、荧光原位杂交、细菌的代谢组学和转录组学分析等现代微生态研究技术，这些技术的应用可以帮助更深入地了解胃生态系统组成及其在健康和疾病中的作用，更好地理解微生物与宿主之间复杂的相互关系。使用 PCR 扩增的 16S rDNA 片段的温度梯度凝胶电泳研究表明，胃内存在丰度较高的肠球菌、链球菌、葡萄球菌、假单胞菌和口腔球菌等菌属。

四、幽门螺杆菌与其他胃微生物的关系

人体内的微生物群落不仅与宿主相互作用，微生物群落之间也相互作用。H. pylori 与其他胃微生物群之间存在错综复杂的关系。H. pylori 能够改变自身的微环境，H. pylori 产生大量尿素酶，可以分解尿素产生氨和碳酸氢盐，这不仅可以改变周围微环境的 pH 值，还可以作为其他微生物群落的代谢底物。H. pylori 可诱导细胞因子和抗菌肽的产生，这些细胞因子和抗菌肽会引起慢性胃炎，并可能抑制胃环境中的其他微生物。胃生态中的其他细菌也会影响 H. pylori 的生长，乳杆菌对 H. pylori 的生长有拮抗作用，链球菌是胃生态中的共生菌，可以拮抗 H. pylori 的生长，并且诱导其球形变。由于胃生态系统的结构影响因素很多，因此需要进一步的实验来确定 H. pylori 与其他胃微生物群之间的确切关系，更好地了解 H. pylor 在胃内环境及相关疾病中的作用。

五、胃微生态与临床疾病的关系

（一）胃生态与慢性胃炎和消化性溃疡病

H. pylori 与慢性胃炎及消化性溃疡之间的病因学联系已得到充分证实。胃生态中的其他微生物在胃、十二指肠疾病中的作用的研究较少，但是，有研究提示即使在没有 H. pylori 的情况下，其他的胃微生物群落，例如链球菌属过度增殖，也可能导致胃炎。

也有研究表明胃内链球菌与消化性溃疡病之间存在显着相关性。这都提示胃内非 H. pylori 细菌通过复杂的机制和相互作用，在胃、十二指肠疾病的发病机制中发挥作用。

（二）胃生态与胃癌

几个大规模前瞻性流行病学干预研究证实了 H. pylori 与胃癌的病因学关系。近年来发表的国内外共识均推荐通过根除 H. pylori 降低胃癌发展的风险。有研究表明除了 H. pylori 外，宿主和环境因素也与胃癌易感性增加有关，H. pylori 与人类共同存在了数千年，只有1%的感染者会发展为胃癌。这也说明胃癌发生是多因素共同作用的结果。

更多研究表明，胃生态中非 H. pylori 微生物群落在胃癌的发生中起着重要作用。这些群落在胃腔内过度增长，通过各种机制，如促进炎症、刺激细胞增殖、产生有毒代谢物等加强 H. pylori 致癌作用。有研究表明，在胃癌患者中胃微生物群的多样性是减低的，胃微生物群的多样性随着从非萎缩性胃炎到肠上皮化生和肠型胃癌的进展而减少。但也有研究结果并不一致，由于新型生物计算工具在评估胃微生物群结构和相互作用方面的不断应用，未来对此问题的理解可能有突破性的进展。

（三）胃生态与其他上胃肠外疾病

胃微生物群与上消化道外疾病之间的相互关系越来越受到关注。有研究表明急性胃肠道感染是感染后肠易激综合征和感染后功能性消化不良的病因。过去几年的多个大规模研究提示 H. pylori 与结直肠肿瘤之间具有相关性，证实 H. pylori 感染会增加结肠肿瘤的风险。另外有研究发现胃微生物群（尤其是 H. pylori）与血液系统疾病，如特发性血小板减少性紫癜和贫血、心血管疾病、神经系统疾病、内分泌疾病，以及皮肤病之间可能存在关联，根除 H. pylori 可以促进这些疾病的缓解。

六、小结

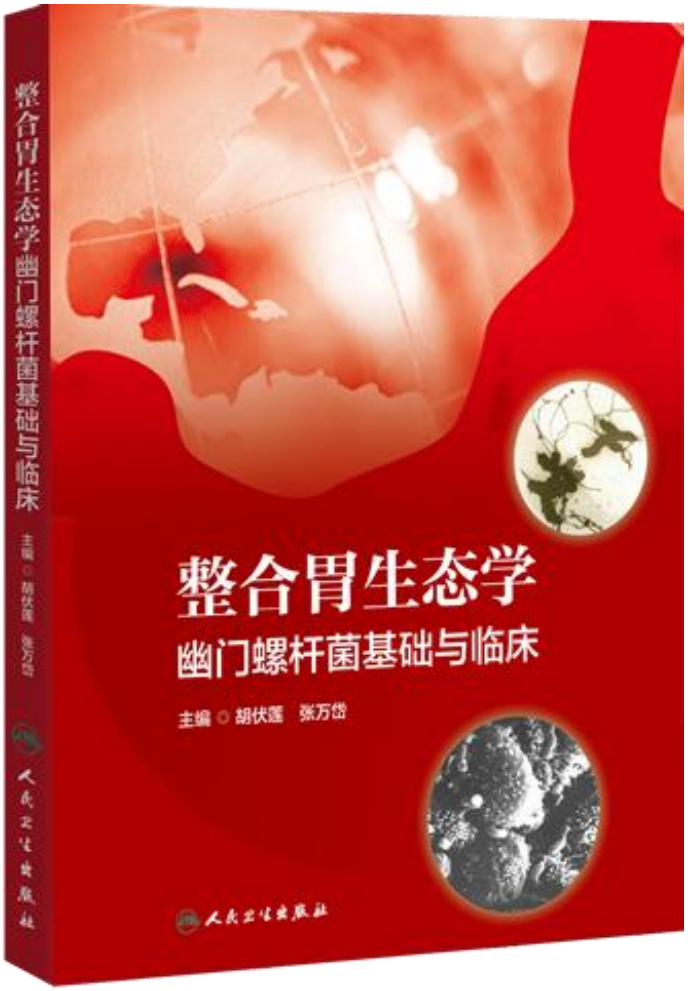
1. H. pylori 的发现颠覆了胃内无菌的观点。人们对胃生态的认识取得了巨大进展，从胃内无菌观点进展到更加复杂和动态的胃生态系统观点，并不断深入研究胃内常驻的微生物群落之间和微生物群落与宿主之间的相互作用。H. pylori 是胃生态中最主要的菌落，但肯定不是唯一的菌落。

2. 越来越多的证据表明 H. pylori 和胃内其他细菌可能具有一定保护作用。胃内原籍微生物菌群的丧失可能增加过敏性疾病、代谢性疾病，以及肿瘤的发生率。也有研究发现 H. pylori 感染可能与食管腺癌、哮喘和肥胖呈负相关。

3. H. pylori 可引起一系列临床疾病，作为胃生态中明确的“罪魁祸首”也可能在维持胃生态动态平衡时发挥某些作用，提示在干预胃微生态的组成时要从整合医学角度进行处理。

4. 总之：任何疾病的处理，都应该以整合医学为原则，以循证医学为证据，强调治病个体化才是医生治病成功的关键。

参考文献:杨志平，樊代明. 整合医学的理论解析. 中华医学杂志, 2016, 96(4): 247-249



从整合医学角度诠释“难治性幽门螺杆菌感染”处理原则和策略

胡伏莲　北京大学第一医院

一、概述

目前幽门螺杆菌 (Helicobacter pylori，下称 H.pylori) 感染的治疗面临着挑战，如何提高 H.pylori 根除率是当前幽门螺杆菌研究的聚焦问题[1]。基于 H.pylori 感染的治疗通常是按 H.pylori“共识”意见处理，本文旨在阐明如何正确理解和运用共识[2]，如何界定“难治性幽门螺杆菌感染”[3]，其处理原则和策略是什么？什么是“幽门螺杆菌治疗新路径”[4]？如何从整合医学角度来处理 H.pylori 感染中的问题？

这不仅是当前 H.pylori 研究的聚焦问题[1]，也是临床医生最关注的问题。

二、幽门螺杆菌治疗现状与挑战

随着 H.pylori 治疗的广泛开展，其耐药性增加，根除率逐渐降低，如何有效地治疗 H.pylori 感染面临着挑战[5，6]。近 20 年来，H.pylori 治疗方案从三联变成四联，疗程从 7 天、10 天延至 14 天。为了克服甲硝唑耐药性，又将其剂量增至 1.6g/日，随着疗程延长，剂量增加，不仅疗效提高有限，而且副作用也随之增加。现在推荐的疗程 14 天标准四联方案，几乎已经成为了当今治疗 H.pylori 的“准则”，尽管如此，但仍有少数患者治疗反复失败。基于随着剂量增加和疗程的延长，其副作用随之增加，所以最新的 Maastricht V 共识[7] 和多伦多的 H.pylori 共识[8] 都仍然推荐标准四联疗法，疗程仍然 14 天。即使失败，也难以增加抗生素剂量和疗程。目前 H.pylori 治疗已处在瓶颈期。寻求符合中国特色的 H.pylori 治疗方案，开创“幽门螺杆菌治疗新路径”[4]是 H.pylori 治疗的必由之路。

三、“共识治疗”与“个体化治疗”

在未涉及到“难治性幽门螺杆菌感染”[3]问题之前，需要首先阐明“共识”与“个体化治疗”之间的对立和统一性[2]

“共识”的重要依据是循证医学，是临床诊断和治疗的基本原则。“共识”与“个体化治疗”从字面看是两个不同的概念，但之间却蕴藏着深刻的内在联系，如果理解或运用有误，可能会导致对病人处理不当。

“共识”本身内含“异议”，所谓“共识”是指将那些存在“异议”的“临床问题”，根据其循证医学证据级别进行“陈述”，然后决定其“推荐等级”而达成“共识”。由于“共识”是具有较高级别的循证医学证据，又得到多数专家的推荐或认可，所以对临床医生具有重要指导作用，尤其对基层医生更为重要。然而在“共识”运用中仍会有不同意见甚至争议[9]，因为“共识”只符合较多的这部份人，并不涵盖所有人。对不符合“共识”意见的病人就应该根据病人的具体情况进行“个体化治疗”。

“个体化治疗”是针对个体施治，基于存在个体差异和地区差异，按“共识”治疗失败者，也证明了“共识”并没有涵盖所有人，而个体化治疗才是成功的关键。

“共识治疗”与“个体化治疗”存在对立性，从整合医学角度，应将“个体化治疗”看成是“共识”的补充和发展。鉴于“共识”存在地区和人群差异，所以国外共识也不能照搬，必须符合国情，因地制宜，对于按“共识”治疗反复失败病人则应该按照“全国中西医整合治疗幽门螺杆菌相关病-证共识”[10]中的“个体化整体治疗”。

四、“难治性幽门螺杆菌感染”的治疗原则和策略

（一）什么叫“难治性幽门螺杆菌感染”[3,10]

H.pylori 感染处理的基本原则通常按照“共识”，但是，并非所有按“共识”治疗者都能成功，少部份病人虽然按照“共识”治疗仍然反复失败，这些按“共识”治疗反复失败者可归属为“难治性幽门螺杆菌感染”[3]。

如何界定“难治性幽门螺杆菌感染”？由于地区和个体差异会出现难治程度的不同，因此很难下一个确切定义，但整体而言必需遵循以下几个原则:（1）在 1-2 年内按“共识”中的“标准四联疗法”治疗失败只少三次以上（包括三次）；（2）每次是不同抗生素，疗程 10-14 天（至少有一次疗程是 14 天）；（3）每次都按“共识”要求完成全疗程；（4）治疗之前必需经过胃镜检查，符合治疗适应证。为什么将失败次数界定为≥3 次？其理由是：①首次治疗，一般选用根除率高、安全性好、符合多数人的方案；②补救治疗，系第 2 次治疗，通常更换抗生素，疗程增至 14 天；③个体化处理，系第 3 次治疗，需要根据药敏试验选择敏感抗生素。

治疗 3 次失败之后，抗生素调整有限，疗程已延至极限，治疗非常困难，因此，将“难治性幽门螺杆菌感染”界定为治疗失败≥3 次。

（二）“难治性幽门螺杆菌感染”处理原则和策略

对“难治性幽门螺杆菌感染”者怎么办？这时应该改变治疗策略，进行“个体化治疗”。所谓“个体化治疗”是针对每一个体辨证施治，不是千人一方，万人一药，应该按照“全国中西医整合治疗幽门螺杆菌相关病-证共识”[10]进行“个体化整体治疗”。

1.“难治性幽门螺杆菌感染”病人于治疗前必需进行“个体化整体评估”[10]

对治疗反复失败的病人，由于 H.pylori 对抗生素的自我保护而球形变，因而导致根除失败，为了使其恢复活性，应暂停抗 H.pylori 治疗 3-6 个月（所谓刹车），但除了暂停抗 H.pylori 治疗之外，还必需同时进行“个体化整体评估”，以作好下一次根除 H.pylori 的治疗前准备，然后进行标准的抗 H.pylori 治疗。“个体化整体评估”是下次治疗方案的选择原则，是经验治疗的依据。

评估内容包括宿主因素、菌株因素、治疗因素、环境因素及生活习惯等，尤其以下应逐个评估：①主要失败原因（如细菌耐药性、病人依从性、对常用抗生素过敏史，特别是青霉素、不良生活习惯等）；②是否高龄、或存在严重躯体疾病等；③是否存在反复治疗而导致的胃肠菌群失衡、明显消化道症状；④是否存在明显的胃黏膜病变（萎缩、肠化、黏膜内瘤变）；⑤是否存在 H.pylori1 球形变而发生的生物学行为改变，特别定植在胃体 H.pylori 不易被根除；⑥既往治疗方案、治疗时机是否恰当；⑦其他因素如：宿主 CYP2C19 基因多态性对质子泵抑制剂代谢的影响、药物相互作用、H.pylori1 菌株类型及毒力的影响等。

2.“难治性幽门螺杆菌感染”相关疾病的“个体化的整体治疗”[10]。

对“难治性幽门螺杆菌感染”的经验治疗是“标本兼治的分阶段综合疗法”[10,11]。

第一阶段：治疗前准备,此阶段治疗目的是梳理病人不利于接受标准治疗的状况，如病人有肠道菌群失调应调整菌群，有明显消化道症状者，应缓解症状，以便增加病人接受标准治疗时的依从性。也可服用中药辨证论治。在准备阶段用药时间和药物因人而异，但一律不可使用抗生素及任何对 H.pylori1 有抑制作用的药物。病人症状缓解后停药至少两周，于治疗前必须重复 13/14C-UBT 检测，确定为阳性者才能进入第二阶段治疗。

第二阶段：含抗生素的标准治疗。

第三阶段：巩固疗效的个体化治疗，对仍有症状者应对症治疗，对治疗中发生过肠道菌群失调者可以服用益生菌两周。

五、幽门螺杆菌治疗新路径

治疗 H.pylori1 有两个途径[4]：一是抗生素直接杀灭作用；二是非抗生素药物的作用：除了现已临床应用的 PPI 和铋制剂以外,“幽门螺杆菌治疗新路径”是指中医中药[10,11,12,13]、益生菌[10,14,15,16,]、胃黏膜保护剂[10,16,17,18,]等非抗生素类药物对 H.pylori 的治疗作用，目前已有一系列基础和临床研究证实非抗生素类药物在 H.pylori 相关疾病治疗中具有良好作用[4,10]：联合含抗生素的标准三联或四联能提高 H.pylori 根除率，减少治疗中不良反应，缩短抗生素疗程，联合非生素类药物的个体化整体治疗也符合整合医学理念。

在当前 H.pylori 治疗面临着挑战的情况下，尤其对“难治性幽门螺杆菌感染”治疗更显示其重要性，因而“全国中西医整合治疗幽门螺杆菌相关病-证共识”于 2018 年 8 月 4 日正式发布[10]，该共识是中西医整合治疗 H.pylori 的第一个共识，也是整合医学领域中的第一个共识,该共识是 H.pylori 治疗旅程的一个拐点，标志着 H.pylori1 治疗已进入一个新阶段。当然新共识还需要更多的基础和临床研究证实或验证，使其合理应用于临床。

六、小结

1.按“共识”治疗反复失败≥3 次者，归属为“难治性幽门螺杆菌感染”。

2.对“难治性幽门螺杆菌感染”于治疗前必需进行“个体化整体评估”，而后进入“个体化整体治疗”，这才是治疗成功的关鍵。

3.“全国中西医整合治疗幽门螺杆菌相关病-证共识”不仅是 “难治性幽门螺杆菌感染”治疗的主要策略，而且符合整合医学理念，体现了中国治疗 H.pylori 特色 。

4.“幽门螺杆菌治疗新路径”是 H.pylori 治疗必由之路，不仅提高 H.pylori 根除率，减少治疗中的副作用，缩短抗生素疗程，而且也是对 H.pylori 耐药性的挑战。

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幽门螺杆菌感染新型原代人胃上皮细胞模型的建立

米阳[1, 2]，高爽[1, 2]，刘行凡[1, 2]，任飞飞[1]，刘斌[1, 2]，郑鹏远[1, 2]

1.郑州大学第五附属医院马歇尔医学研究中心，河南郑州

2.郑州大学医学科学院

摘要

目的　培养三维（3D）人胃黏膜上皮类器官，转为二维（2D）原代胃黏膜细胞培养，并建成人 2D 原代胃上皮细胞的幽门螺杆菌感染模型。

方法　（1）从正常人胃上皮组织中分离胃腺，在含有多种生长调节和凋亡抑制等混合因子的培养基中，依附于基质胶而培养成 3D 类器官；（2）　利用免疫荧光技术鉴定胃上皮类器官的相关分子标记；(3) 研究正常原代胃上皮细胞被幽门螺杆菌感染后的形态学变化，利用免疫印迹技术鉴定幽门螺杆菌感染相关蛋白的表达水平。

结果　成功培养出可长期传代的人胃上皮 3D 类器官，具有典型的人胃黏膜上皮分子标记。而且 3D 类器官转为 2D 平面培养的原代胃上皮细胞，可作为幽门螺杆菌的体外原代细胞感染模型。

结论　3D 胃上皮类器官，可作为 2D 原代胃上皮细胞的持久来源，为研究幽门螺杆菌感染人体胃上皮的分子机制带来个体化的新模型。

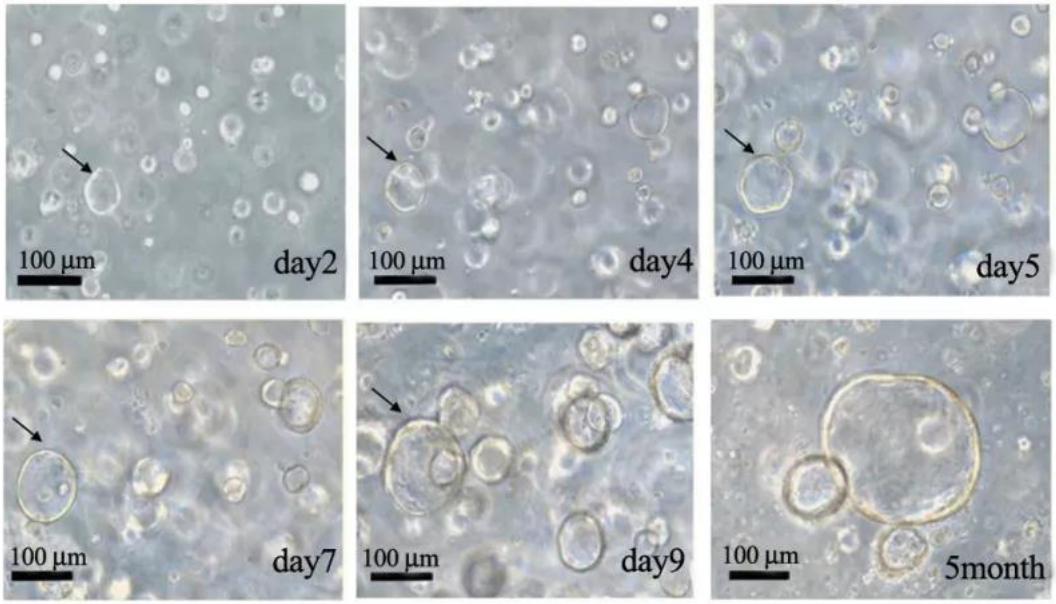
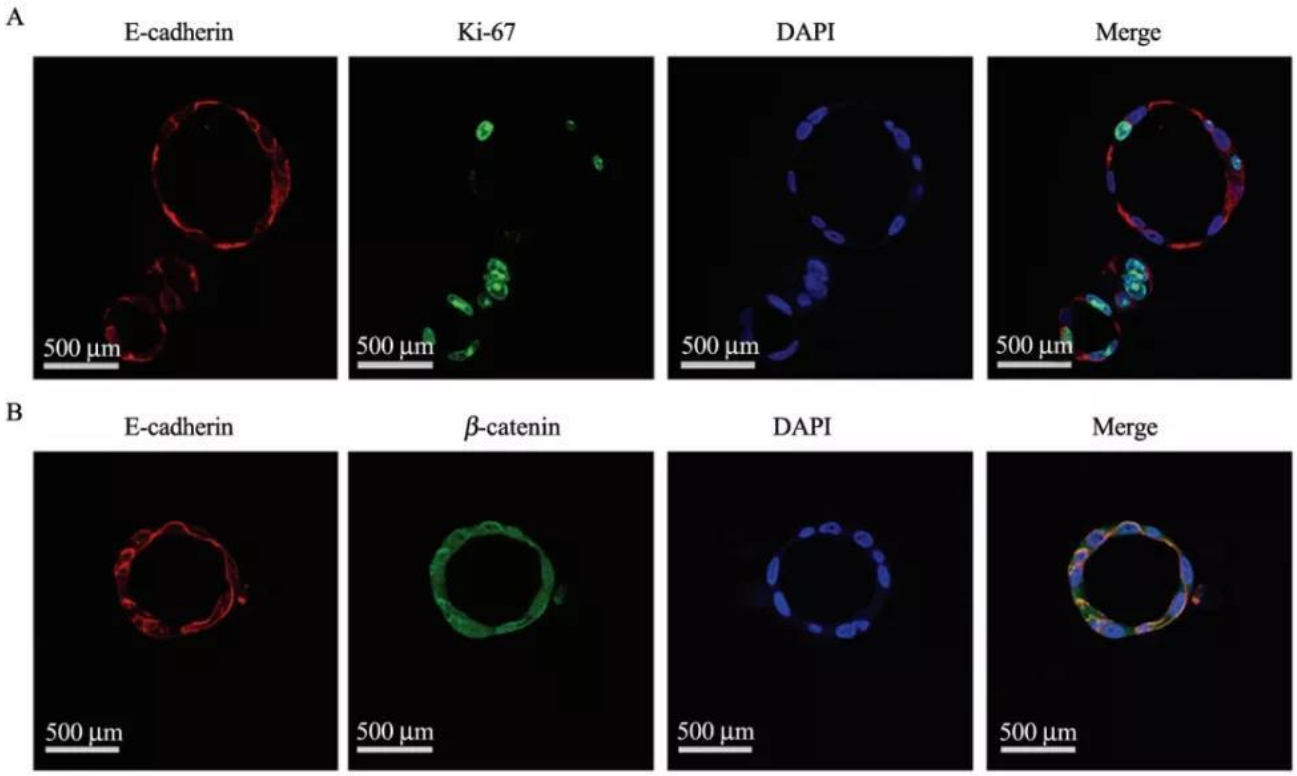


图 1　胃上皮 3D 类器官球状体在体外持续传代增殖（普通显微镜下照片）



注：A 代表胃上皮分子标记 E-cadherin、增殖标记 Ki-67；B 代表胃上皮分子标记 E-cadherin、β-catenin、细胞核染色 DAPI 以及 Merge 共定位的免疫荧光照片。

图 2　胃上皮 3D 类器官球状体的分子特征（共聚焦显微镜下照片，横切面）

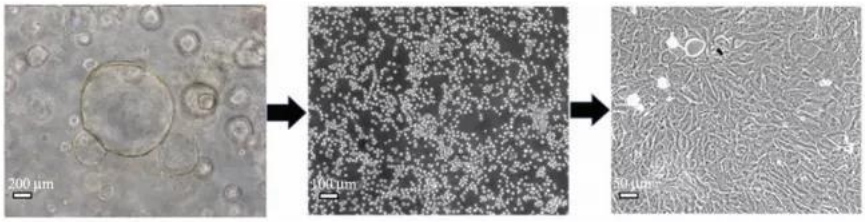
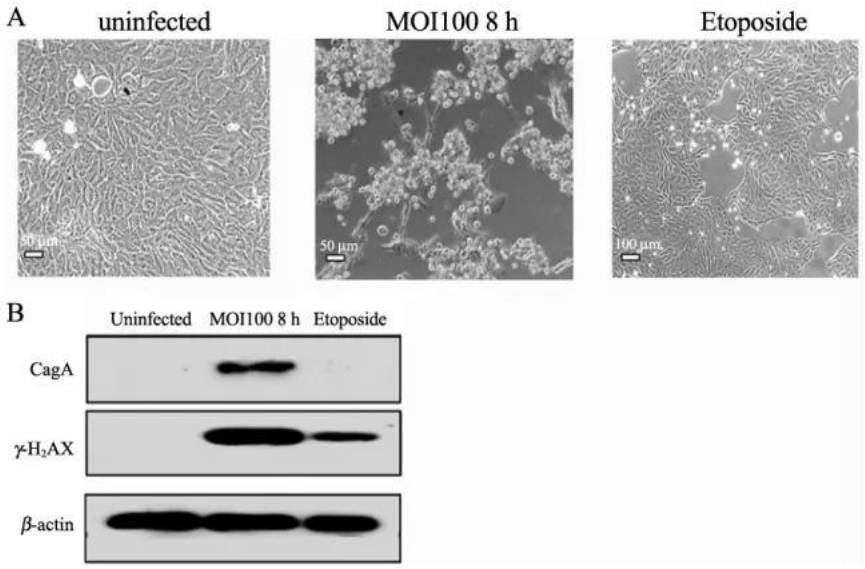


图 3　胃上皮 3D 类器官转为 2D 培养（普通显微镜下照片）



注：A 为感染前后的 2D 原代胃上皮细胞，Uninfected 为未感染，Etoposide 为依托泊苷处理组；B 为感染前后免疫印迹结果，CagA为细胞毒素相关蛋白，γH_2AX 为 DNA 损伤标志物。

图 4　幽门螺杆菌感染 2D 人原代胃上皮细胞的细胞（普通显微镜下照片）和分子表型变化

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布拉氏酵母菌散联合三联疗法对幽门螺杆菌感染根除效果的前瞻性多中心随机对照研究

杨桂彬 胡伏莲 成虹 高文 盛剑秋 张振玉 杜奕奇 左秀丽 李岩 陈烨 王邦茂 赵子涵

作者单位：100049 航天中心医院消化科（杨桂彬、赵子涵）；北京大学第一医院消化科（胡伏莲、成虹、高文）；解放军总医院第七医学中心（盛剑秋）；南京市第一医院消化科（张振玉）；海军军医大学附属长海医院消化科（杜奕奇）；山东大学附属齐鲁医院消化科（左秀丽）；中国医科大学附属盛京医院消化科（李岩）；南方医科大学附属南方医院消化科（陈烨）；天津医科大学总医院消化科（王邦茂）

通信作者：胡伏莲，Email: djjyhu@163.com

摘要

目的 观察布拉氏酵母菌散联合三联疗法作为一线方案对幽门螺杆菌(H. pylori)感染的根除治疗效果及安全性。

方法 选取 2019 年 8 月至 2020 年 1 月全国 9 个中心接受胃镜检查并诊断非溃疡性消化不良患者（NUD）患者共 540 例，采用前瞻性、随机对照多中心临床研究方法，纳入患者随机分为 3 组，A 组（布拉氏酵母菌散四联组）：布拉氏酵母菌散+三联疗法（10d 后继续予布拉氏酵母菌至 14 天）；

B 组：铋剂四联组（疗程 10d）；C 组：三联疗法组。患者均在停药 28 d 后进行 13C 尿素呼气试验检测 H. pylori。分别对比 H. pylori 根除率、14 天及 44 天症状改善情况和不良反应。

结果 最终 497 共入组例患者，其中 472 例完成试验。意向性分析(ITT)： A 组根除率为 77.8%(126/162)，B 组根除率 80.1%(137/171)；C 组 H. pylori 根除率为 65.2%(107/164)。符合方案分析：A 组根除率为 79.7%(126/158)，B 组根除率 86.2%(137/159)；C 组 H. pylori 根除率为 69.0%(107/155)。三组患者间 ITT 及 PP 分析差异均有统计学意义（P<0.01）。各组两两比较，ITT 及 PP 分析 A、B 组之间均无统计学意义（P>0.05），A 组和 B 组与 C 组比较差异均有统计学意义（P<0.05）。在第 14 天时 A、B 组腹胀、嗳气及上腹痛症状评分缓解程度较 C 组有显著差异（P<0.05）。第 44 天 A 组症状总评分缓解程度较 B、C 组有统计学意义（P<0.05），其中 A 组腹胀、嗳气症状评分缓解程度较 B、C 组有统计学差异（P<0.05）。所有入组患者均无严重不良反应事件发生。A 组在腹泻发生率明显低于另外两组（P<0.05）

结论 布拉氏酵母菌散联合三联疗法作为一线方案对初次治疗的非溃疡性消化不良的 H. pylori 感染均能获得较好的根除效果，并在症状缓解上有优势，具有较好的耐受性和临床安全性。

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ORIGINAL ARTICLE

Clinical Trials Study

Modified Xiaochaihu Decoction for gastroesophageal reflux disease: A randomized double-simulation controlled trial

Zhe Li, Lin Tao, Sheng-Sheng Zhang, Xiao-Hong Sun, Su-Ning Chen, Jing Wu

ORCID number: Zhe Li 0000-0001-6343-3055; Lin Tao 0000-0002-9260-4287; Sheng-Sheng Zhang 0000-0003-1986-3511; Xiao-Hong Sun 0000-0003-1941-6148; Su-Ning Chen 0000-0002-2967-3597; Jing Wu 0000-0002-8355-1953.

Author contributions: Li Z and Tao L contributed equally to this manuscript; summary and drafting of the manuscript were completed by Li Z and Tao L; the experiment was performed by all authors; acquisition, analysis, and interpretation was conducted by Li Z and Tao L; a critical review of the manuscript was conducted by Li Z, Tao L, and Zhang SS; All authors read the manuscript and approved the final version.

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Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Beijing Hospital of Traditional Chinese Medicine of Capital Medical University (Approval No. 2018BL-026-02)

Zhe Li, Lin Tao, Sheng-Sheng Zhang, The Digestive Center, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing 100010, China

Xiao-Hong Sun, Department of Digestive, Peking Union Medical College Hospital, Beijing 100730, China

Su-Ning Chen, Department of Digestive, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Jing Wu, Department of Digestive, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Corresponding author: Sheng-Sheng Zhang, PhD, Chief Doctor, The Digestive Center, Beijing Hospital of Traditional Chinese Medicine Capital Medical University, No. 23 Art Gallery Back Street, Dongcheng District, Beijing 100010, China. zhangshengsheng@bjzhongyi.com

Abstract

BACKGROUND

Gastroesophageal reflux disease (GERD) has a high prevalence worldwide, and its incidence is increasing annually. Modified Xiaochaihu Decoction (MXD) could relieve the symptoms of GERD, but the effects of MXD on GERD manifestations and relapse prevention need to be further explained. Therefore, we performed a prospective, double-blind, and double-simulation study.

AIM

To verify the efficacy of MXD for GERD and its effect on esophageal motility.

METHODS

Using randomization, double-blinding, and a simulation design, 288 participants with GERD were randomized to the treatment group and control group and received herbs (MXD) plus omeprazole simulation and omeprazole plus herbs simulation, respectively, for 4 wk. The GERD-Q scale score and esophageal manometry were measured at baseline, after treatment, and at 1 mo and 3 mo follow-up visits when medication was complete to evaluate recurrence indicators.

RESULTS

The GERD-Q scale score in both groups decreased significantly compared to those before treatment ($P < 0.01$). However, no significant difference was observed

Clinical trial registration statement: This study is registered at: www.chictr.org.cn/; The registration identification number is ISRCTN17685397.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Grade E (Poor): 0

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between the two groups ($P > 0.05$). Esophageal manometry showed that participants with lower esophageal sphincter pressure reduction and the proportion of ineffective swallowing (more than 50%) improved in both groups from baseline ($P < 0.01$), especially in the treatment group ($P < 0.05$). The percentage of small intermittent contractions, large intermittent contractions, and increased pre-phase contractions in the treatment group significantly improved compared with baseline ($P < 0.05$) but did not improve in the control group ($P > 0.05$). There was no significant difference between the groups after treatment ($P > 0.05$). The percentage of weak esophageal contractility (distal contractile integral < 450 mmHg·s·cm), improved in both groups ($P < 0.01$), but no significant difference was observed between the groups after treatment ($P > 0.05$). The relapse rate in the treatment group was lower than that in the control group at the 1 mo ($P < 0.01$) and 3 mo follow-up ($P < 0.05$).

CONCLUSION

MXD has a similar therapeutic effect to omeprazole in mild-to-moderate GERD. The therapeutic effect may be related to increased pressure in the lower esophageal sphincter and reduced ineffective swallowing.

Key Words: Gastroesophageal reflux disease; Traditional Chinese medicine; Esophageal sphincter pressure; Gastroesophageal reflux disease-Q scale score; Modified Xiaochaihu Decoction

Core Tip: This multicenter, randomized, double-blind, double-simulation study proved that Modified Xiaochaihu Decoction has a similar therapeutic effect to omeprazole in the treatment of patients with typical symptoms of gastroesophageal reflux disease and reflux esophagitis grades A and B. Modified Xiaochaihu Decoction was superior to omeprazole in improving lower esophageal sphincter resting pressure and reducing ineffective esophagus swallowing. The recurrence rate of symptoms was significantly lower than that of omeprazole within 1 mo and 3 mo after completing treatment. Modified Xiaochaihu Decoction may be an alternative treatment to proton pump inhibitor maintenance in patients with gastroesophageal reflux disease.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) has a high prevalence worldwide, and its incidence is increasing annually[1]. Impaired esophageal and gastric motor function as well as reduced resting pressure of the lower esophageal sphincter are considered to be involved in the pathogenesis of GERD. Chemical drugs can help relieve the symptoms and eliminate inflammation, but the relapse rate is high. It is reported that esophagitis and other symptoms are 80% and 90%, respectively, 6 mo after proton pump inhibitor (PPI) withdrawal[2]; therefore, many patients require long-term maintenance medication. Our previous observations showed that Modified Xiaochaihu Decoction (MXD) could relieve the symptoms of GERD[3]. The present study aimed to evaluate the effects of MXD on GERD manifestations and relapse prevention and to determine its underlying mechanism, from the aspect of esophageal motion, using a prospective, double-blind, and double-simulation design compared with omeprazole.

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MATERIALS AND METHODS

Patients

This is a prospective, double-blind, and double-simulation study, which was sponsored by Beijing Hospital of Traditional Chinese Medicine of Capital Medical University and conducted in Peking Union Medical College Hospital, Beijing Shijitan Hospital of Capital Medical University, and Shengjing Hospital of China Medical University from January 2015 to December 2019.

Ethical permission

The study was reviewed and approved by the Ethics Committee of Beijing Hospital of Traditional Chinese Medicine of Capital Medical University. The trial registration number is ISRCTN17685397.

Diagnostic criteria

Participants who met the standard of the "Chinese Experts Opinion on Gastroesophageal Reflux Disease"[2] were considered for inclusion in the study.

The inclusion criteria were: (1) patients aged 18-65 years; (2) satisfied the diagnostic criteria for GERD; and (3) GERD-Q score ≥ 8, with A-B esophagitis under gastroscopy.

Exclusion criteria were: (1) a history of gastric, esophageal, and duodenal surgery; (2) presence of Zollinger-Ellison syndrome or primary esophageal motility disease; (3) suspected or confirmed to have a malignant disease or have early warning symptoms; (4) use of PPI or H2 receptor blockers within 2 wk before enrollment; (5) serious primary heart, liver, lung, kidney, pancreas, or other serious diseases that would affect their survival; (6) disabled patients (blind, deaf, dumb, mentally retarded, mentally disabled, physically disabled) as required by law; (7) suspected or confirmed history of alcohol and drug abuse; (8) allergies, such as those with a history of allergies to two or more drugs or food; or known allergies to the ingredients of MXD; and (9) pregnant and lactating women.

Sample size estimation

The sample-size calculation in this design was based on a non-inferiority test with a 1:1 comparison principle. Using the one-sided test, according to previous literature reports and research results, the formula: [n1 = n2 = 2 (Z_{α} + Z_{β}) 2P (1-P)/δ2, Z_{α} = 1.645, Z_{β} = 0.845, P = 0.65, δ = -0.15; n1 = n2 approximately 125] was used. In this study, the expulsion rate was designed to be 15%, the sample content required for each group was 144, and a total of 288 samples were required.

Randomization and allocation concealment

Randomization into the treatment or control group was performed with a 1:1 allocation ratio. Balanced treatment assignments were achieved by block randomization. This process was performed using SAS 9.4 software to generate a random sequence. The block length was eight. Now that there were four units and a total of 288 subjects, each unit was assigned 72 connecting consecutive codes and the corresponding allocation to treatment or control.

Participants in the treatment group were given herbal granules (2 packets/d, one packet at a time with 200 mL water, before meals) combined with omeprazole simulation tablets produced by Jiangyin Tianjiang Pharmaceutical Co., Ltd. The traditional Chinese medicine (TCM) prescriptions were mainly composed of *Bupleurum* 10 g, *Codonopsis* 15 g, fried *Atractylodes* 12 g, *Coptis chinensis* 10 g, *Flos* insulae 10 g, and fried Raphani 15 g. Omeprazole placebo was produced by Lunan New Times Pharmaceutical Co., Ltd.) and was taken orally, 20 mg each time, once on an empty stomach in the morning.

Participants in the control group were given omeprazole enteric-coated tablets combined with an herbal granule placebo. The herbal granule placebo was produced by Jiangyin Tianjiang Pharmaceutical Co., Ltd. The simulated MXD placebo contained 2.5% of the dose of the original formula, with a color correction agent, seasoning agent, starch, dextrin, and other auxiliary materials added. After spray drying, crushing, screening, mixing, granulation, and packaging, the granule simulation agent was placed in bags. The appearance, characteristics, and odor were the same as those of the actual herbal medicine and contained 10.3 g/bag (produced by Jiangyin Tianjiang Pharmaceutical Co., Ltd.). Omeprazole enteric-coated tablets (Lunan New Times Pharmaceutical Co., Ltd., SFDA approval No. 008140505) were taken orally, 20 mg each time, once on an empty stomach in the morning.

All medications in both groups were administered for 4 wk, and all participants had a washout period of 2 wk before taking the medication.

Blinding

The blind codes were sealed separately and kept by those who were not directly involved in this clinical trial. Doctors and patients were blind to the medicine. The medicine and placebos were packaged in the same outer packaging, and their appearance, color, and characteristics were consistent. Both were made by the same manufacturer.

Esophageal manometry

The ManoScan360TM gastrointestinal dynamic high-resolution esophageal manometry system (Given Imaging, United States) and a solid-state surrounding pressure measuring electrode catheter with 36 pressure measuring channels was used. Adjacent channels were spaced 1 cm apart, and each channel had 12 surround pressure points. The recorded data were analyzed with ManoView Analysis software.

The patient underwent a high-resolution manometry test after fasting for at least 8 h, and the pressure-measuring catheter was inserted through the nasal cavity. The depth of the catheter was adjusted so that the display screen showed two high-pressure areas at the proximal and distal ends of the esophagus, the upper esophageal sphincter, and the lower esophageal sphincter (LES), and the catheter was fixed at the nasal wing. During the examination, the patient was placed in the supine position and adapted for 5 min. The basal pressure level in the esophagus was recorded, and the patient swallowed 10 times with 5 mL each time. The interval between two swallows was at least 30 s, and the patient remained awake throughout the recording.

Study endpoints

Primary endpoints: The primary endpoint of this study was the GERD-Q scale score. Positive symptom scoring may reflect the frequency of heartburn and reflux symptoms and scored 0, 1, 2, 3 points according to "0 d," "1 d," "2-3 d," or "4-7 d" with a maximum score of 6 points. Negative symptom scoring may reflect the frequency of central abdominal pain and nausea and scored 3, 2, 1, 0 points according to "0 d," "1 d," "2-3 d," or "4-7 d" with a maximum score of 6. Positive impact scoring may reflect the frequency of heartburn or reflux affecting sleep and the frequency of patients taking extra over-the-counter drugs such as antacids and scored 0, 1, 2, 3 points according to "0 d," "1 d," "2-3 d," and "4-7 d" with a maximum score of 6 points. The highest total score of the 6 questions was 18 points. Scores were recorded before medication and at the second and fourth weeks of medication, and follow-up scores were recorded at the first and third month after medication was complete.

Secondary endpoints: Lower esophageal sphincter pressure (LESP), the percentage of ineffective swallowing > 50%, percentage of small peristaltic interruption, percentage of large peristaltic interruption, distal contractile integral (DCI), and percentage of early contractions were the secondary endpoints. As not all participants in the study had abnormal esophageal manometry indicators, only those with abnormalities at baseline were measured before and after completion of medication. Indices of esophageal manometry were recorded before and 4 wk after treatment.

Follow-up

Follow-up was performed at 1 mo and 3 mo after completion of medication, and the number and percentage of patients who were not on medication, on maintenance medication, intermittent medication, and on-demand medication were recorded in the treatment group and the control group.

Statistical analysis

SAS9.4 software (Beijing Hospital of TCM Version, Order Number: 9C1XJD) was used for statistical analysis. mean ± SD were used to describe the continuous variables. Frequency and percentage were used to describe the categorical variables. Statistical tests were performed using the bilateral test, and a P value < 0.05 was considered statistically significant. Measurement data were analyzed using the t-test or Wilcoxon rank-sum test. For comparisons within groups, the paired t-test or Wilcoxon signed-rank test was used. For comparisons between groups, categorical variables were analyzed using the χ^2 test and Fisher's exact test, and continuous variables were analyzed using analysis of variance if normally distributed, or using the nonparametric test if non-normally distributed. For repeated measurements at several time

points between groups, the repeated measures analysis of variance or the generalized estimating equation was used.

RESULTS

Patient characteristics

A total of 288 patients were included in this study and were divided into the treatment group and the control group, with 144 cases in each group. Twenty-eight patients in the treatment group were excluded, including 1 patient with adverse reactions (systemic pruritus after taking the medicine, and the symptoms subsided after 2 d of withdrawal), 14 cases left the study due to personal reasons, and 13 cases left due to dissatisfaction with the treatment; of the 14 patients excluded in the control group, 9 patients left the study due to personal reasons, 5 patients left due to dissatisfaction, and a total of 246 patients completed the study (Figure 1).

One hundred and sixteen patients were included in the treatment group, 50 males and 66 females, aged 18-65 years, with an average age of 50.30 ± 10.38 years. Disease course ranged from 1 mo to 36.67 years. One hundred and thirty patients were included in the control group, 64 males and 66 females, aged 24-65 years, with an average age of 50.48 ± 11.71 years. Disease course ranged from 2 mo to 20 years. There were no statistically significant differences between the two groups of patients in terms of gender, age, and duration of illness.

GERD-Q scale scoring

There were significant differences ($P < 0.01$) within the treatment group in relation to withdrawal of medication before treatment and treatment at 2 wk, 4 wk, 1 mo, and 3 mo. In the control group there were significant differences ($P < 0.01$) in relation to withdrawal of medication before treatment compared with treatment at 2 wk, 4 wk, 1 mo, and 3 mo. There were no significant differences between the treatment group and the control group during treatment and follow-up visits (Table 1).

Indicators of esophageal manometry

With regard to post-treatment changes in patients with reduced LESP before treatment, post-treatment LESP was higher than pre-treatment LESP in both the treatment group and control group, and there was a significant difference between the groups ($P < 0.01$); there was also a significant difference between the two groups after treatment ($P < 0.01$) (Table 2 and Figure 2).

Changes in patients with small intermittent contractions

The post-treatment proportion of small intermittent contractions in the treatment group was reduced compared with that before treatment, and the difference was statistically significant ($P < 0.05$). There was no significant difference within the control group before and after treatment ($P > 0.05$), and there was no significant difference between the two groups after treatment ($P > 0.05$) (Table 3).

Changes in patients with increased large intermittent contractions

The post-treatment proportion of large intermittent contractions in the treatment group was reduced compared with that before treatment, and the difference was statistically significant ($P < 0.05$). There was no significant difference within the control group before and after treatment ($P > 0.05$), and there was no significant difference between the two groups after treatment ($P > 0.05$) (Table 4).

Changes in patients with ineffective swallowing > 50%

The post-treatment proportion of ineffective swallowing in the treatment group and control group was reduced compared with that before treatment. The difference was statistically significant in the two group ($P < 0.01$), and the difference was statistically significant in the two groups after treatment ($P < 0.05$) (Table 5).

Changes in patients with pre-phase contractions

The post-treatment proportion of pre-phase contractions in the treatment group was reduced compared with that before treatment, and the difference was statistically significant ($P < 0.05$). There was no significant difference within the control group before and after treatment ($P > 0.05$), and there was no significant difference between the two groups after treatment ($P > 0.05$) (Table 6).

Table 1 Gastroesophageal reflux disease-Q scale scoring changes

	Treatment, *n* = 116	Control, *n* = 130	Mean difference (95% confidence interval)	*P* value
Before treatment	10.53 ± 2.01	10.10 ± 1.64	0.434 (0.067 to 0.077)	0.077
2 wk treatment	8.25 ± 1.85[a]	7.99 ± 1.85[a]	0.266 (0.100 to 0.112)	0.108
4 wk treatment	7.36 ± 1.71[a]	7.21 ± 1.63[a]	0.147 (0.463 to 0.483)	0.469
1 mo withdrawal	7.59 ± 1.82[a]	7.59 ± 1.47[a]	0.003 (0.301 to 0.309)	0.301
3 mo withdrawal	7.56 ± 1.78[a]	7.44 ± 1.54[a]	0.114 (0.826 to 0.841)	0.837

[a]$P < 0.01$, 2 wk treatment, 4 wk treatment, 1 mo of withdrawal, 3 mo of withdrawal were compared with before treatment.

Table 2 Changes in patients with reduced lower esophageal sphincter pressure

	Treatment, *n* = 39	Control, *n* = 41	*P* value
Pre-treatment, mmHg	7.99 ± 2.92	8.26 ± 2.97	0.646
Post-treatment, mmHg	16.15 ± 4.90[a,b]	13.23 ± 3.71[a]	0.003
Mean difference (95% confidence interval)	-8.158 (0.000 to 0.000)	-4.917 (0.000 to 0.000)	
P value	0	0.000[a]	

[a]$P < 0.01$, compared with pre-treatment in the group.
[b]$P < 0.05$, compared with the control group after treatment.

Table 3 Changes in patients with small intermittent contractions

	Treatment, *n* = 52	Control, *n* = 49	*P* value
Pre-treatment, %	30.48 ± 10.39	33.67 ± 9.50	0.077
Post-treatment, %	27.11 ± 8.47[b]	29.79 ± 8.77	0.063
Mean difference (95% confidence interval)	3.365 (0.035 to 0.043)	3.469 (0.057 to 0.066)	
P value	0.037	0.051	

[b]$P < 0.05$, compared with pre-treatment in the group.

Table 4 Changes in patients with large intermittent contractions

	Treatment, *n* = 7	Control, *n* = 9	*P* value
Pre-treatment, %	22.85 ± 7.55	18.88 ± 6.00	0.261
Post-treatment, %	17.14 ± 4.87[b]	15.55 ± 5.27	0.529
Mean difference (95% confidence interval)	5.714 (0.119 to 0.132)	3.333 (0.237 to 0.254)	
P value	0.046	0.083	

[b]$P < 0.05$, compared with pre-treatment in the group.

Changes in patients with DCI less than 450 mmHg·s·cm

The post-treatment value of DCI in the treatment group and control group both increased compared with the values before treatment, and the difference was statistically significant in the group ($P < 0.01$). There was no significant difference in the two groups after treatment ($P > 0.05$) (Table 7).

Table 5 Changes in patients with ineffective swallowing > 50%

	Treatment, *n* = 49	Control, *n* = 48	*P* value
Pre-treatment, %	85.30 ± 15.42	83.12 ± 17.03	0.647
Post-treatment, %	63.46 ± 21.07[a,b]	72.29 ± 21.52[a]	0.016
Mean difference (95% confidence interval)	21.837 (0.000 to 0.000)	10.833 (0.002 to 0.004)	
P value	0	0.003	

[a]$P < 0.01$, compared with pre-treatment in the group.
[b]$P < 0.05$, compared with the control group after treatment.

Table 6 Changes in patients with increased pre-phase contractions

	Treatment, *n* = 21	Control, *n* = 25	*P* value
Pre-treatment, %	24.52 ± 8.04	26.00 ± 8.16	0.503
Post-treatment, %	19.04 ± 6.24[b]	23.20 ± 7.48	0.052
Mean difference (95% confidence interval)	5.476 (0.025 to 0.032)	2.800 (-1.894 to 7.494)	
P value	0.035	0.23	

[b]$P < 0.05$, compared with pre-treatment in the group.

Table 7 Changes in patients with distal contractile integral less than 450 mmHg·s·cm

	Treatment, *n* = 23	Control, *n* = 23	*P* value
Pre-treatment, mmHg·s·cm	237.80 ± 87.62	243.97 ± 86.53	0.373
Post-treatment, mmHg·s·cm	417.53 ± 128.22[b]	400.26 ± 136.63[b]	0.111
Mean difference (95% confidence interval)	-179.731 (0.000 to 0.000)	-156.283 (0.000 to 0.000)	
P value	0	0	

[b]$P < 0.05$, compared with pre-treatment in the group.

Efficacy in reducing recurrence rate

Patients were followed up at 1 mo after completing treatment, and a significant difference was observed between the treatment group and the control group ($P < 0.01$) (Table 8).

Patients were followed up at 3 mo after completing treatment, and a significant difference was observed between the treatment group and the control group ($P < 0.05$) (Table 9).

DISCUSSION

This multicenter, randomized, double-blind, double-simulation study proved that MXD has a similar therapeutic effect to omeprazole in the treatment of patients with typical symptoms of GERD and reflux esophagitis grades A and B. MXD was superior to omeprazole in improving LES resting pressure and reducing ineffective esophagus swallowing. The recurrence rate of symptoms was significantly lower than that of omeprazole within 1 mo and 3 mo after completing treatment. MXD may be an alternative treatment to PPI maintenance in patients with GERD.

GERD-Q scale scoring has high diagnostic accuracy in GERD and can evaluate quality of life and treatment response[4-6]. The results of this study showed that the GERD-Q scale scores in the two groups revealed significant changes before and after treatment, while there was no significant difference between the two groups indicating that MXD and the PPI omeprazole had equivalent clinical efficacy in improving the

Table 8 Follow-up results at 1 mo after completing treatment, *n* (%)

	Treatment, *n* = 116	Control, *n* = 130	*P* value
Not on medication	97 (83.6)[b]	86 (66.2)	0.002
Maintenance medication	12 (10.3)	16 (12.3)	-
Intermittent medication	1 (0.9)	14 (10.8)	-
On-demand medication	6 (5.2)	14 (10.8)	-

[b]$P < 0.05$, compared with pre-treatment in the group.

Table 9 Follow-up results at 3 mo after completing treatment, *n* (%)

	Treatment, *n* = 116	Control, *n* = 130	*P* value
Not on medication	85 (73.3)[b]	71 (54.6)	0
Maintenance medication	14 (12.1)	25 (19.2)	
Intermittent medication	6 (5.2)	9 (6.9)	
On-demand medication	11 (9.5)	25 (19.2)	

[b]$P < 0.05$, compared with pre-treatment in the group.

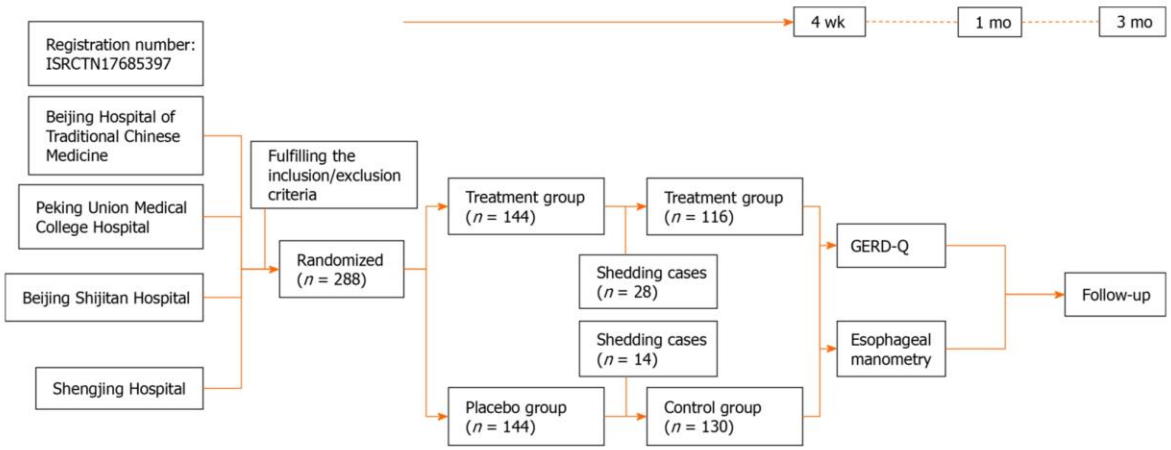

Figure 1 Study flow chart. GERD: Gastroesophageal reflux disease.

symptoms of GERD.

Esophageal dysfunction is a common cause of GERD. Abnormal dysfunction is mainly reflected in the weakened esophageal anti-reflux barrier function and esophageal clearance function. This study only compared abnormal esophageal motility indicators before and after treatment to explore the possible mechanism of MXD in the treatment of GERD. The results showed that MXD increased the LES resting pressure, enhanced the esophageal barrier effect, reduced ineffective contractions to improve esophageal clearance, reduced pre-phase contractions to adjust the coordination of esophageal movement, and improved esophageal clearance function. LES is an important component of the esophageal anti-reflux barrier, and its pressure is higher than that in the stomach to prevent the reflux of gastrointestinal content into the esophagus. It has been confirmed that LESP in GERD patients is significantly lower than in normal individuals[7]. When LESP decreases, the contents of the stomach and duodenum are more easily refluxed into the esophagus.

The research by Hu *et al*[8] showed that LES pressure decreases with the severity of acid reflux, and the decrease in LESP results in a significant increase in the incidence of hiatal hernia. Food in the esophagus is mainly propelled by peristalsis. When

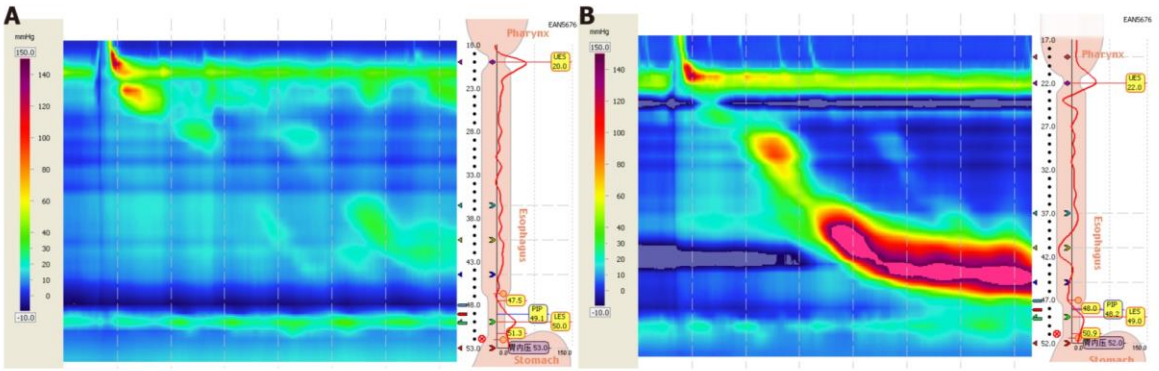

Figure 2 High-resolution esophageal manometry before and after treatment. The results in A and B were from the same patient in the treatment group. A: High-resolution esophageal manometry before treatment; B: High-resolution esophageal manometry 3 mo after treatment.

peristalsis is interrupted, the transmission and clearance functions of the esophagus in terms of the food bolus and reflux content are impaired, resulting in weakened clearance of the esophagus. Ribolsi *et al*[9] confirmed that esophageal peristalsis interruption in patients with GERD is associated with increased acid exposure in the supine position and increased reflux clearance time.

The Chicago esophageal dyskinesia classification released in 2015 defined swallowing with DCI < 450 mmHg·s·cm as ineffective swallowing and ineffective esophageal motility as > 50% of ineffective swallowing[10]. Frequent ineffective peristalsis of the esophagus can lead to impaired esophageal clearance and prolong the exposure duration of the food bolus and reflux content in the esophagus[11], thereby stimulating reflux symptoms. Liu *et al*[12] showed that GERD symptoms were closely related to DCI and ineffective esophageal peristalsis. With the widespread application of pH monitoring, the results of existing research show that ineffective esophageal peristalsis will lead to longer reflux time in both the supine and upright position and prolong average acid clearance time[8,13]. In addition, the pre-phase contractions of the esophagus will block passage of the food bolus and impair the peristaltic function of the esophagus. If the food bolus remains in the esophagus for an extended period, it will also increase stimulation of the esophageal mucosa. It can be inferred that MXD improved the patients' symptoms *via* the above effects.

The difficulty in the treatment of GERD lies in its high recurrence rate. Some studies have shown that in patients with GERD who take PPIs for 4-8 wk that the recurrence rate is 26.0%-47.8%, and the recurrence rate is 30.4% during the 1 year follow-up[14-16]. The follow-up visits in the present study were conducted at 1 mo and 3 mo after completing treatment. Patients not on medication, on maintenance medication, intermittent medication, and on-demand medication were assessed. It was found that the recurrence rate following TCM was low, and its ongoing efficacy was significantly better than omeprazole. The results of this study indicated that by increasing the resting pressure of the LES, improving ineffective swallowing, and reducing pre-phase contractions, the mechanism of reflux is partially corrected, and MXD can lower the recurrence rate.

It is generally accepted that the pathophysiology of GERD mainly involves inflammation and the immune response[17-19]. Modern pharmacological studies have shown that MXD has anti-inflammatory, antioxidant, and immunomodulatory activity. Saikoside, the active component of bupleurum has significant anti-inflammatory, immunoregulatory, and neuroregulatory effects[20]. Studies have shown that saikoside can significantly reduce the expression of tumor necrosis factor-α, interleukin-1, and interleukin-6 and can inhibit the production of nitric oxide, thereby contributing to its anti-inflammatory effects, and saikoside is an effective NF-κB channel inhibitor[21,22]. Studies have shown that inulin fructan extracted from the roots of Codonopsis has anti-inflammatory and anti-oxidant effects. Li *et al*[23] studied the protective effect of inulin fructan on ethanol-induced acute gastric ulcers in rats, and the results showed that inulin fructan significantly increased the activity of superoxide dismutase and glutathione peroxidase in gastric tissue in a dose-dependent manner and reduced the content of malondialdehyde and nitric oxide, thereby protecting the gastric mucosa. In addition, the active component Berberine from *Coptis chinensis* also has similar anti-inflammatory and antioxidant effects[24], and it has been shown that Berberine has a killing effect on *Helicobacter pylori*[25].

CONCLUSION

This study had the following limitations: the research only compared clinical symptoms, and pH monitoring before and after treatment was not carried out. In addition, the treatment duration was 4 wk, which was insufficient. It is considered that the course of treatment should be extended to 8 wk as this would be more conducive to symptom relief and resolution of inflammation. The next phase in this research is to extend the course of treatment and carry out in-depth observations on the effect of MXD on acid reflux.

In the present study, the number of drop-outs in the TCM group was higher, most of which were due to severe acid-refractory heartburn symptoms, and the TCM did not take effect quickly. Due to the double-blind and double-simulation design of the study, we believe that the results objectively demonstrate the effects of MXD and omeprazole on clinical symptoms and esophageal dynamics in GERD patients and provide evidence-based data for GERD patients to receive further treatment. Therefore, it is recommended that patients with reflux symptoms without serious or reflux esophagitis belonging to class A-B be treated with TCM, and for patients with severe symptoms of acid reflux and heartburn, which require quick relief, both Chinese and Western medicine is suggested to obtain more satisfactory efficacy.

ARTICLE HIGHLIGHTS

Research background

Gastroesophageal reflux disease (GERD) has a high prevalence worldwide, and its incidence is increasing annually. According to the preliminary experiment of the research group, Modified Xiaochaihu Decoction (MXD) could relieve the symptoms of GERD.

Research motivation

The effects of MXD on GERD manifestations and relapse prevention need to be further explained. Therefore, we performed a prospective, double-blind, and double-simulation study.

Research objectives

To verify the efficacy of MXD for GERD and its effect on esophageal motility.

Research methods

Using randomization, double-blinding, and a simulation design to compare the GERD-Q scale score and esophageal manometry between patients under the treatment of MXD (treatment group) and omeprazole (control group).

Research results

In total, 288 patients were divided into the treatment group and control group. The GERD-Q scale score in both groups decreased significantly compared to those before treatment ($P < 0.01$). However, no significant difference was observed between the two groups ($P > 0.05$). Esophageal manometry showed that participants with sphincter pressure reduction and the proportion of ineffective swallowing (more than 50%) improved in both groups from baseline ($P < 0.01$), especially in the treatment group ($P < 0.05$). The percentage of small intermittent contractions, large intermittent contractions, and increased pre-phase contractions in the treatment group significantly improved compared with baseline ($P < 0.05$) but did not improve in the control group ($P > 0.05$). The percentage of weak esophageal contractility (distal contractile integral < 450 mmHg·s·cm) improved in both groups ($P < 0.01$). The relapse rate in the treatment group was lower than that in the control group at the 1 mo ($P < 0.01$) and 3 mo follow-up ($P < 0.05$).

Research conclusions

MXD has a similar therapeutic effect to omeprazole in mild-to-moderate GERD. The therapeutic effect may be related to increased pressure in the lower esophageal sphincter and reduced ineffective swallowing.

Research perspectives

Our results supported that MXD has a similar therapeutic effect to omeprazole in mild-to-moderate GERD and could improve esophageal motility.

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Berberine-Loaded Carboxylmethyl Chitosan Nanoparticles Ameliorate DSS-Induced Colitis and Remodel Gut Microbiota in Mice

Luqing Zhao[1], Xueying Du[2], Jiaxin Tian[2], Xiuhong Kang[1], Yuxin Li[1], Wenlin Dai[3], Danyan Li[1], Shengsheng Zhang[1] and Chao Li[2]**

[1]Digestive Disease Center, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China, [2]State Key Laboratory of Chemical Resource Engineering, Beijing University of Chemical Technology, Beijing, China, [3]Center for Applied Statistics, Institute of Statistics and Big Data, Renmin University of China, Beijing, China

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***Correspondence:**
Shengsheng Zhang
zhangshengsheng@bjzhongyi.com
Chao Li
lichao@mail.buct.edu.cn

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Inflammatory bowel disease (IBD) is a refractory disorder characterized by chronic and recurrent inflammation. The progression and pathogenesis of IBD is closely related to oxidative stress and irregularly high concentrations of reactive oxygen species (ROS). A new oxidation-responsive nano prodrug was constructed from a phenylboronic esters-modified carboxylmethyl chitosan (OC-B) conjugated with berberine (BBR) that degrades selectively in response to ROS. The optimized micelles exhibited well-controlled physiochemical properties and stability in a physiological environment. OC-B-BBR micelles could effectively encapsulate the anti-inflammatory drug berberine and exhibit ideal H_2O_2-triggered release behavior as confirmed by *in vitro* drug loading and release studies. The *in vivo* anti-inflammatory effect and regulation of gut microbiota caused by it were explored in mice with colitis induced by dextran sodium sulfate (DSS). The results showed that OC-B-BBR significantly ameliorated colitis symptoms and colon damage by regulating the expression levels of IL-6 and remodeling gut microbiota. In summary, this study exhibited a novel BBR-loaded Carboxylmethyl Chitosan nano delivery system which may represent a promising approach for improving IBD treatment.

Keywords: berberine, nanoparticles, colitis, drug delivery, gut microbiota

INTRODUCTION

Inflammatory bowel disease (IBD) is a refractory gastrointestinal disorder characterized by chronic and recurrent inflammation. Ulcerative colitis (UC) and Crohn's disease (CD) are the two main forms of IBD (Kaser et al., 2010). IBD has a high incidence in the United States (more than 1 million) and in Western Europe (2.5 million), and has evolved into a widespread disease with increasing prevalence all over the world (Kaplan, 2015). The pathogenesis of IBD is still not fully understood, but it is mainly considered to be associated with environmental factors, host genetic susceptibility, changes in intestinal flora and intestinal epithelial barrier dysfunction, and other factors (Zundler and Neurath, 2015). Oxidative stress plays an essential role in the pathogenesis and progression of IBD (Tian et al., 2017), and leads to excessive ROS accumulation. Biopsies from patients with IBD demonstrate abnormally high levels of ROS at the site of the lesion, with mucosal ROS concentrations increasing from 10- to 100-fold (Simmonds et al., 1992; Lih-Brody et al., 1996).

Although there is no clear evidence of a relationship between IBD and mortality, there is no doubt that IBD has an adverse impact on the quality of life of patients. Many drugs are available for the treatment of UC including 5-Aminosalicylic acid, steroids, immunosuppressant, probiotics, biological agents, herbal medicines, and so on. Ulcerative colitis can be cured with FMT in patients who do not respond to other more accessible treatments. However, IBD is difficult to cure permanently at present. Taking medicine inevitably brings about many adverse reactions and consumes a lot of medical resources (Shivaji et al., 2019; Wilke et al., 2020).

Berberine (BBR) is an isoquinoline alkaloid, often used as an antidiarrheal, derived from the rhizome of *Coptis chinensis* ("Huang-Lian" in Chinese) of the Ranunculaceae family. Recently, BBR and its derivatives have been examined for use in IBD treatment (Massironi et al., 2013; Wakuda et al., 2013). It is worth noting that BBR may alleviate intestinal inflammation through different mechanisms. It seems to be related to the regulation of the Treg/Th17 balance by modifying gut microbiota (Cui et al., 2018). In addition, BBR could identify bitter taste receptors on intestinal Tuft cells and activate IL-25-ILC2-IL-13 immune pathway to impair damaged intestinal tract by promoting differentiation of intestinal stem cells (Xiong et al., 2021). There is also a broad space to improve the efficacy and bioavailability of BBR. For example, its absolute bioavailability has been reported to be less than 1% (Chae et al., 2008; Chen et al., 2011) and the plasma level of BBR is very low, although the significant pharmacological effects of BBR have been observed in clinic (Hua et al., 2007).

A targeted drug delivery system can ensure that the drug is released only at the intestinal inflammation site instead of healthy tissue. Targeting and selectivity are achieved by the abnormally high concentration of ROS in the inflammation site (Wilson et al., 2010; Zhang et al., 2016). Because the nanosized targeted delivery system will mainly accumulate in the inflamed part of the intestine, it is considered to be an excellent idea for the treatment of IBD (Lamprecht et al., 2001). Santos' group reported a nano-in-micro composite to achieve an oxidation-responsive delivery of rifaximin (RIF) for IBD treatment. RIF mediates changes in epithelial cell physiology and reduces bacterial attachment and internalization, and also antagonized the effects of tumor necrosis factor-α on intestinal epithelial cells by activating pregnane X receptor, which inhibits nuclear factor-κB-mediated proinflammatory mediators and induces detoxification genes. RIF-loaded nanoparticles have been prepared by phenylboronic esters-modified dextran (OxiDEX). Under physiologically relevant H_2O_2 concentrations, the nanoparticles exhibited a high degree of H_2O_2-responsive degradation ability and controlled drug release (Bertoni et al., 2018). Nanoparticles are likely to adjust the properties of drugs, such as stability, solubility, and release ability, and their surface is easily modified to introduce targeting ligands, and even adjust surface characteristics, including surface charge and adhesion properties. Consequently, we here proposed a functional prodrug micelle as an inflammation-targeted drug, which was comprised of BBR covalent linked to biocompatible carboxylmethyl chitosan by aryl boronic ester as responsive linker. This nanosystem was adopted so that chitosan-based prodrug micelles could effectively deliver berberine to inflamed tissue by ROS responsive mechanism, improving its bioavailability in the specific site (**Figure 1**). Compared with the RIF-loaded delivery system, BBR in the current system was covalently linked to the carrier by unique catechol group, which can precisely achieve ROS-responsive and prevent the premature release of drugs in the delivery process. The synthesis and physiochemical properties of polymeric OC-B-BBR were explored to optimize micelle structure. The ability of the system to release berberine in physiological and simulated ROS overexpression medium was also investigated. *In vivo* anti-inflammatory effect and regulation of gut microbiota by it were explored in mice with colitis induced by dextran sodium sulfate (DSS), which showed features in common with ulcerative colitis in humans.

MATERIALS AND METHODS

Materials

Carboxylmethyl chitosan (OC, Mw = 37 kDa, degree of deacetylation = 88.7%) was purchased from Macklin. Berberine (BBR) was purchased from Saen Chemical Technology Co., Ltd. The Spectra/Por 1 dialysis membrane (MWCO: 3,500) was purchased from Spectrum Laboratories. All the other reagents and solvents were provided by Beijing Chemical Reagent Co., Ltd. and used without further purification. A Bruker AV-400 nuclear magnetic resonance spectroscope was used to record all NMR spectra at 400 MHz in $CDCl_3$ (unless otherwise specified). An Agilent 6540 UHD Q-TOF MS (analyzed ions up to m/z 6,000) equipped with a gas nebulizer probe was used to record data of High-resolution mass spectra (HRMS). DSS was purchased from MP Biomedicals Co., Ltd. TNF-α and IL-6 enzyme-linked immunosorbent assay (ELISA) kits were purchased from Wuhan servicebio technology Co., Ltd. TGF-β and IL-23 ELISA kits were purchased from Multisciences (LIANKE) Biotech Co., Ltd.

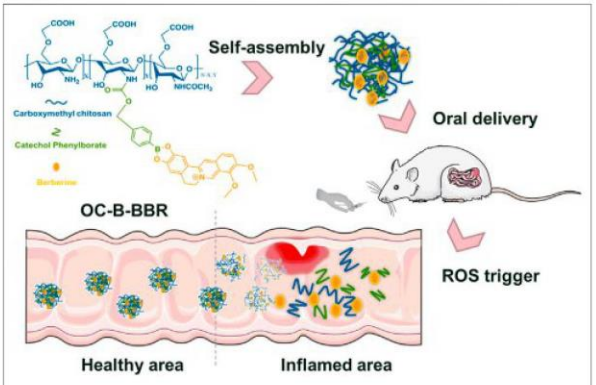

FIGURE 1 | The schematic presentation of OC-B-BBR prodrug micelles structure and their inflamed-selective anti-inflammatory drug delivery by ROS-triggered mechanism.

Preparation of OC-B-BBR Micelles

Phloroglucinol (2.5 g, 19.8 mmol) was dissolved in 60% H_2SO_4 (50 ml) and stirred at room temperature until the raw materials were completely dissolved to form a colorless solution. Berberine (2.5 g, 7.4 mmol) was added to the above solution, and the mixture was stirred at 95°C for 15 min. Then the reaction was transferred to the saturated NaCl solution and stirred at room temperature for 2 h. The solution was filtered, and the filter cake was dissolved with methanol. The resulted solution was concentrated *in vacuo* and washed by ethyl acetate for twice. The solution was then filtered again, upon which the compound demethyleneberberine was obtained as a dark red solid (yield 90%). 1H-NMR (400Mz, DMSO-d_6): δ/ppm = 3.105–3.136 (t, 2H, - CH_2), 4.070 (s, 3H, - CH_3), 4.095 (s, 3H, - CH_3), 4.898–4.929 (t, 2H, - CH_2), 6.884 (s, H, Ph-H), 7.557 (s, H, Ph-H), 8.052–8.075 (d, H, Ph-H), 8.173–8.196 (d, H, Ph-H), 8.768 (s, H, Ph-H), 9.432 (bs, H, -OH), 9.857 (s, H, Ph-H), 10.246 (bs, H, -OH).

We dissolved carboxymethyl chitosan (OC, 128 mg, 0.24 mmol) and 0.2 ml of tetramethylguanidine in 15 ml deionized water, then stirred the mixture for 30 min 4-nitrophenyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl]methyl ester (NBC, 0.2 g, 0.501 mmol) was dissolved in 5 ml THF, which was added dropwise to the above mixture at 25°C. After the reaction was finished, the solution was dialyzed against water for 2 days. The product OC-B was obtained by lyophilization.

The OC-B-BBR micelles were prepared using dialysis method. In brief, OC-B (20 mg) was dissolved in 8.4 ml deionized water and saturated $NaHCO_3$ was added to adjust pH = 8. Then 3 ml DMA was added to the above solution with stirring for 10 min at room temperature. 10 mg of demethyleneberberine dissolved in methanol (2 ml) were slowly added to the mixture, then stirred for 8 h at 25°C. The resulting solution was dialyzed against water/methanol (1,000 : 2, v/v) for 2 days (molecular weight cut off 3,500 Da) to remove by-products, and then lyophilized to obtain a dry reddish brown flocculent product of OC-B-BBR micelles (60 mg).

Characterization of Physiochemical Properties

Gel permeation chromatography (GPC) (TDK 302, Viscotek, USA) was used to determine the molecular weight distribution of the analytes, in which the mobile phase was water. A Zetasizer Nano instrument (Zetaplus, Brookhaven, USA) and a HeeNe laser (633 nm) were used to measure the particle size of micelles by dynamic light scattering (DLS) to collect optical measurements. All analytes were suspended in pH 7.4 PBS at a concentration of 1 mg mL^{-1} in DLS measurement. S-4700 cold field emission scanning electron microscope (SEM, Hitachi, Japan) was used to analyze the surface morphology of polymeric products and obtain SEM images. Double-sided tape was used to mount the sample for SEM to the metal post, and a thin layer of gold was sputtered under vacuum. For zeta potential measurement, a Nano-ZS ZEN3600 particle sizer (Malvern Instruments) was used.

The encapsulation efficiency (EE) and loading capacity (LC) of OC-B-BBR micelle were depicted as **Eqs. 1** and **2**, respectively.

$$\mathrm{EE}\,(\%) = \frac{\text{weight of Barberine in micelle}}{\text{weight of Barberine feed}} \times 100\% \quad (1)$$

$$\mathrm{LC}\,(\%) = \frac{\text{weight of encapsulated Berberine}}{\text{total weight of micelle}} \times 100\% \quad (2)$$

In Vitro Drug Release of Micelles

A dialysis membrane was used to evaluate the release of OC-B-BBR micelles under sink conditions. For simulated ROS released study, H_2O_2 with different concentrations was added into phosphate-buffer solution (PBS, pH 7.4) as the release media. In brief, 2 mg of OC-B-BBR micelles (DS = 13.1%) were kept in a dialysis bag (MWCO: 3.5 kDa), sealed and placed in 200 ml of release medium, and continuously shook at 100 rpm at 37°C. 1 ml of buffer solution was collected at various time intervals, and 1 ml of fresh medium was added in time after each collection. The cumulative amounts of berberine were determined by Waters Alliance HPLC (UV-detector, λ = 360 nm, C-18 column, eluent: 0.2% phosphoric acid in water: acetonitrile (36:64, v/v), flow rate: 1.0 ml min^{-1}).

Animal Experiments and Dosage Information

Animal experiments were designed according to ARRIVE 2.0 Guideline. C57BL/6 J mice aged 6–8 weeks were obtained from the SPF (Beijing) Biotechnology Co., Ltd (permission number: SCXK (jing) 2019–0,010). The mice were cultured under standard conditions (temperature of 20–26°C, relative humidity of 40–70%, light-dark cycle of 12/12 h, clean bedding, free access to water, and standard dry pellet diet). After a week of adaptive feeding, the mice were randomly divided into four groups, with eight mice in each group. The groups were as follows: 1) Control group, continually fed water alone for 10 days; 2) DSS group, colitis was induced with 3% DSS, which was added to their drinking water for 6 days, on the fourth day, started to use normal saline for gavage for 7 days; 3) OC-B-BBR group, colitis was induced with 3% DSS, which was added to their drinking water for 6 days, on the fourth day, started to use nano-berberine for gavage (30 mg $kg^{-1}\cdot d^{-1}$) for 7 days; 4) Mesalazine group, colitis was induced with 3% DSS for 6 days, on the fourth day, started to use mesalazine for gavage (100 mg kg^{-1}) for 7 days.

Animal studies were performed according to the NIH Guide for the Care and Use of Laboratory Animals and were approved by Animal Care and Use Committee of Beijing Hospital of traditional Chinese Medicine, Capital Medical University.

Disease Activity Index (DAI)

The body weight, stool viscidity, and fecal occult blood were observed daily, and the DAI (Yan et al., 2018) of the mice were measured, including body weight loss (the percentage of weight loss relative to the initial body weight, where 0 score = none, 1 score = 1%–5%, 2 score = 5%–10%, 3 score = 10%–20%, 4 score => 20%),

stool viscidity (0 score = normal, 2 score = loose, 4 score = diarrhea), and fecal occult blood (0 score = no blood, 1 score = +, 2 score = ++, 3 score = +++, 4 score = gross bleeding). DAI = (body mass index + stool viscidity + bleeding)/3.

Sample Collection and Measurement

Colons and spleens were excised from sacrificed mice, and then the length of colons and weight of the spleens were measured. The spleen index = wet weight of the spleen (mg)/the bodyweight (g). Feces were collected for 16 S ribosomal RNA (16SrRNA) analysis. Portions of the colon were fixed in 10% formalin and then embedded in paraffin sections for hematoxylin-eosin (H&E) staining. A portion of that colon was store at -80°Cfor ELISA analysis.

Intestinal Mucosal Injury Index Analysis

The colons were dissected to observe the damages on intestinal mucosa. The extent of the damage was graded by colonic mucosa damage index (CMDI) (Yan et al., 2018), scored as follows: 0, no injury to the colonic mucosa; 1, the surface of intestinal mucosa is smooth, no erosion or ulcer, but with mild hyperemia and edema; 2, has congestion and edema, the mucosa is coarse and granular, with erosion or intestinal adhesion; 3, necrosis and ulcers appeared on the surface of intestinal mucosa, which also has high congestion and edema (the maximum longitudinal diameter of the ulcer is shorter than 1.0 cm), moreover, the intestinal wall surface has necrosis and inflammation or the hyperplasia of intestinal wall; and 4, the maximum longitudinal diameter of ulcer is longer than 1.0 cm, or with total intestinal wall necrosis more severe than 3 points.

Histological Analysis

H&E stained sections of colonic tissue was determined by two independent, blinded investigators following a scoring system for inflammation-associated histological changes in the colon (Wirtz et al., 2007). The scoring system for inflammation-associated histological changes in the colon was: 0, No evidence of inflammation; 1, Low level of inflammation with scattered infiltrating mononuclear cells (1–2 foci); 2, Moderate inflammation with multiple foci; 3, High level of inflammation with increased vascular density and marked wall thickening; and 4, Maximal severity of inflammation with transmural leukocyte infiltration and loss of goblet cells.

ELISA Analysis

Levels of TNF-α (purchased from Wuhan servicebio technology Co., Ltd.), IL-6 (purchased from Wuhan servicebio technology Co., Ltd.), TGF-β (purchased from Multisciences (LIANKE) Biotech Co., Ltd.), and IL-23 (purchased from Multisciences (LIANKE) Biotech Co., Ltd.) in colon tissue were quantified using ELISA kits according to the instructions.

16SrNA Analysis

Magpure stool DNA KF kit B (Magen, China) was used to extract genomic DNA from feces. 30ng of qualified genomic DNA samples and corresponding fusion primers were used to configure the PCR reaction system. The v3-v4 region of 16 S rRNA of genomic DNA was amplified by setting the PCR reaction parameters. The PCR products were purified with agencourt ampure XP magnetic beads, dissolved in elusion buffer, labeled, and completed the establishment of the library. Agilent 2,100 Bioanalyzer was used to detect the fragment range and concentration of the library. According to the size of inserted fragments, hiseq platform was selected for sequencing. After getting off the machine, the data were filtered, and the reads were spliced into tags through the overlap relationship between reads. Under the given similarity, tags were aggregated into out, and the OTU representative sequences were compared with the database by RDP classifer (V2.2) software for species annotation, and the confidence threshold was set to 0.6. Based on OTU and annotation results, species complexity analysis, species diversity analysis, and correlation analysis were carried out.

Statistical Analysis

Multiple groups were compared by one-way analysis of variance (ANOVA). *t*-test or Mann-Whitney *U*-test was used to compare the two groups. Data were expressed as mean ± standard deviation (SD). $p < 0.05$ was considered statistically significant.

RESULTS

Design and Synthesis of Berberine Nanomicelle

Carboxylmethyl chitosan was chosen as a carrier to improve solubility and biocompatibility of micelles for drug delivery. Stimuli-responsive phenyl borate ester as a linker conjugated berberine to carboxylmethyl chitosan by effective aminolysis reaction. The synthesis route of the nanocarrier OC-B-BBR was depicted in **Supplementary Scheme S1**. Initially, NBC was prepared according to previous reports (Jourden and Cohen, 2010; Chung et al., 2018), as a key intermediate for linking glycol chitosan and berberine. Phenyl boronate moiety was linked to 2-NH_2 on carboxylmethyl chitosan by aminolysis, and subsequently borate ester was then easily hydrolyzed under alkaline conditions to give OC-B. A simple strategy was proposed to conjugate berberine by its unique catechol structure. The exposed boronic acid group can spontaneously react with catechol in water to form stable borate ester (OC-B-BBR). The successful synthesis of OC-B-BBR nanocarrier was confirmed by 1H NMR spectra. The characterization of OC and OC-B was also presented as controls to better assign the proton signals of berberine in OC-B-BBR (**Supplementary Figures S1–S3**). The amphiphilic OC-B-BBR conjugates readily formed self-assembled micelles in an aqueous environment. In mild excess ROS environment, the stimuli-responsive borate ester was broken to release berberine molecules.

Physicochemical Properties of Micelles

The physiochemical properties of nanocarriers should be carefully considered to achieve target special delivery of the particles. The primary concerns, including degree of substitute (DS), particle size, encapsulation efficiency (EE), and loading capacity (LC), were determined as shown in **Table 1**. The feed

TABLE 1 | Physiochemical properties of OC, OC-NBC, and OC-B-BBR.

Samples	M_w (Da) ± SD	M_n (Da) ± SD	M_w/M_n ± SD	Particle size (nm) ± SD	PDI[b] ± SD	EE (%)[c] ± SD	LC (%)[d] ± SD
OC	37,695 ± 1,348	17,127 ± 1,123	2.2 ± 0.2	-[a]	-	-	-
OC-NBC	54,985 ± 2,350	22,982 ± 2,140	2.4 ± 0.3	222.7 ± 26.4	0.42 ± 0.12	-	-
OC-NBC-BBR	17,049 ± 929	14,497 ± 827	1.2 ± 0.1	230.2 ± 18.1	0.22 ± 0.09	67.5 ± 4.4	13.1 ± 1.6

[a]*no data.*
[b]*polydispersity index.*
[c]*Encapsulation efficiency, see section Materials and Methods for calculation.*
[d]*Loading capacity, see section Materials and Methods for calculation.*

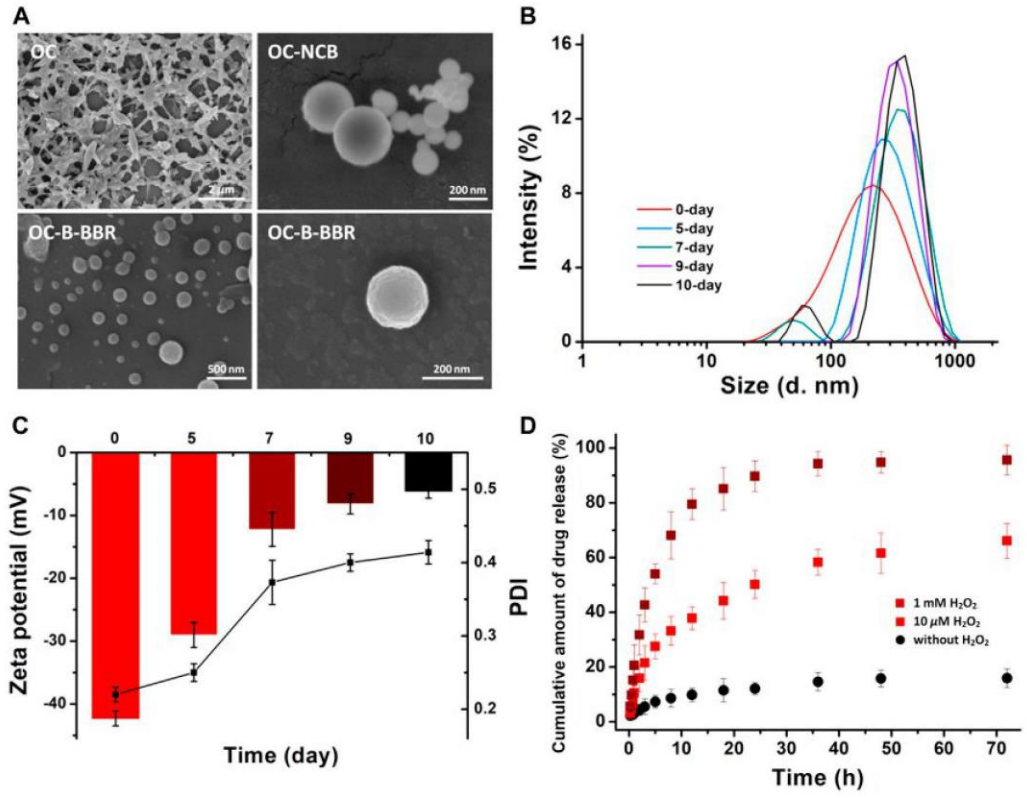

FIGURE 2 | (A) SEM images of the different polymers. **(B)** The changes in OC-B-BBR nanoparticle size in pH 7.4 medium. **(C)** The changes in surface charges and PDI **(D)** *In vitro* drug release profiles of berberine. The OC-B-BBR micelle was incubated in pH = 7.4 buffer without H_2O_2 (black dot), 10 μM H_2O_2 (red square), and 1 mM H_2O_2 (wine square), as measured through HPLC.

ratio of the reaction was changed to adjust the DS of berberine, which can greatly affect the self-assembly behavior and hydrophilic-lipophilic balance of the micelles. Phenyl boronic ester was firstly grafted to OC with different DSs ranged from 10.08 to 26.02%, and the mean diameters of the micelles, measured by DLS, were in the 120–140 nm range. The poor solubility of berberine and reactivity of phenolic hydroxyl (alcoholic hydroxyl was more likely to react with phenylboric acid), to a large extent, limited the increase of DS. The optimized OC-B-BBR (DS = 13.6%) was used to evaluate the subsequent drug release and *in vivo* anti-inflammatory efficacy.

The nanoscale morphology of the obtained structure was shown by electron microscope images. As shown in **Figure 2A** by SEM measurement, OC and blank OC-B were spherical nanoparticles (about 100 nm) and cross-linked. The micelles of OC-B-BBR maintained good microsphere morphology, as shown in **Figure 2A** in different scales. The average particle size of the nanoparticles was about 130 nm, and slightly larger than the

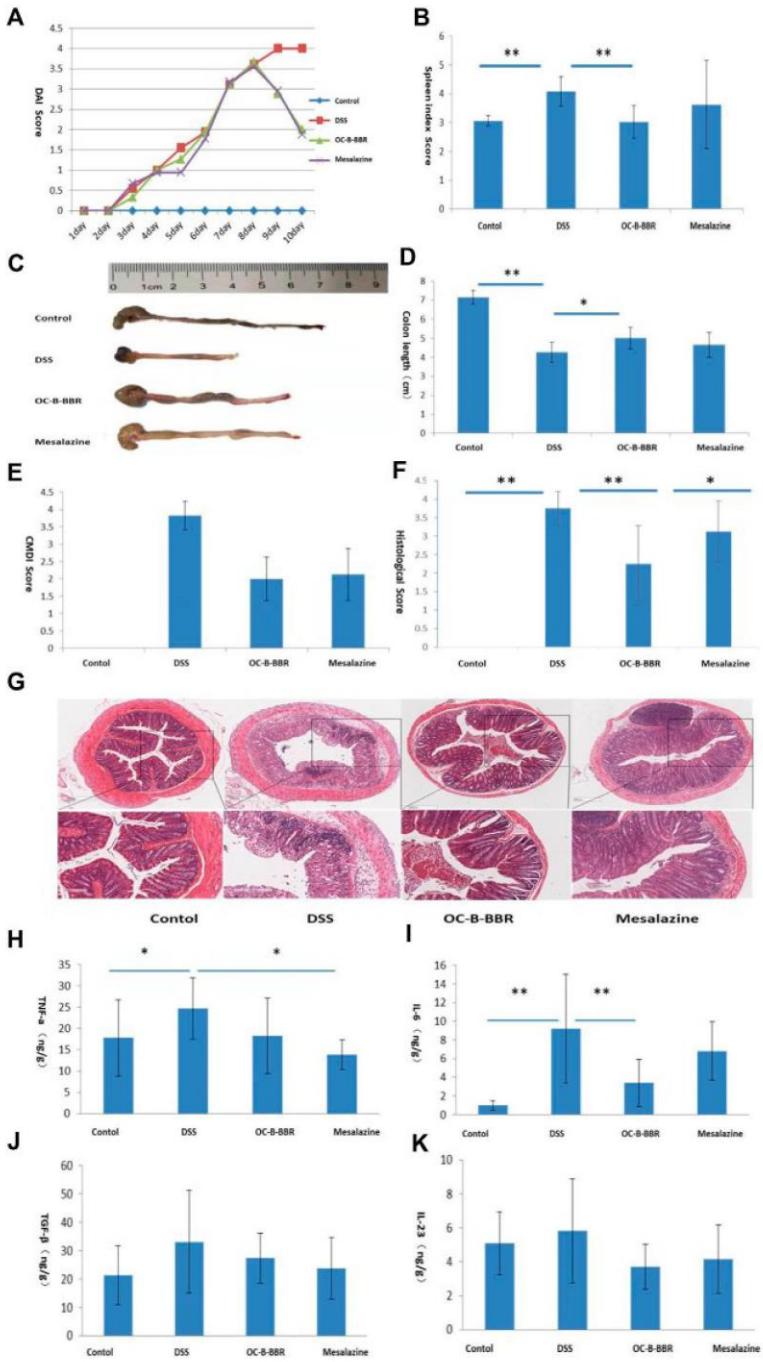

FIGURE 3 | OC-B-BBR ameliorated DSS-induced colitis in mice. Results represent mean ± SD; n = 8, $^{*}p < 0.05$; $^{**}p < 0.01$. **(A)** disease activity indexes (DAI); **(B)** Spleen index; **(C)** Colon picture; **(D)** Colon length; **(E)** Colonic mucosa damage index (CMDI) score; **(F)** Histological score; **(G)** H&E staining of sections displayed colonic tissue damage and leukocyte infiltration, ×4 and ×10; **(H)** TNF-α; **(I)** IL-6; **(G)** TGF-β; **(K)** IL-23.

carrier OC-B. The change trends of particle size measured by DLS were basically the same as that measured by SEM. For the specific data of particle size, the DLS results were slightly larger than the SEM results. This was mainly because the structure was in a hydrated state during DLS measurement, which made the size of the structure larger.

Subsequently, the stabilities of OC-B-BBR micelles were monitored on the basis of variation in sizes and surface charges. In pH = 7.4 medium, the micelles showed insignificant changes in size and a negligible decrease in zeta potential in 5 days (**Figures 2B,C**), suggesting the good stability of the micelles that was essential for a prolonged blood half-life *in vivo*.

In Vitro Drug Release Profile

The drug release profiles in physiological and simulated ROS environment were explored. As shown in **Figure 2D** without H_2O_2, less than 20% berberine was released in 72 h incubation at pH 7.4, indicating that the micelles had satisfactory stability around physiological conditions. When 10 μM H_2O_2 was added in the micelles system, 50% of berberine was collected in 24 h incubation, indicating the ROS-sensitivity of OC-B-BBR micelles. At least 65% of the drugs were released over the tested time. The same assays were performed again with 1 mM H_2O_2 incubation, and the rate of berberine release sharply increased. More than 90% of the drugs can be released in 24 h incubation, showing the sensitivity to excess ROS. The sustained and thorough release indicated that the nanomicelles have a favorable response ability in inflamed tissues with high levels of ROS, which promoted drug delivery efficacy.

OC-B-BBR Showed a Potential Role in Ameliorating the Colitis Induced by DSS in Mice

To study the effect of OC-B-BBR in colitis, five parameters, DAI, colon length, spleen index, CMDI score, and histological score, were evaluated. Mice in the DSS group presented more severe colitis than mice in the OC-B-BBR group, as evidenced by a significant increasing of DAI (**Figure 3A**) and spleen index ($p < 0.01$) (**Figure 3B**), and shortening of the colon ($p < 0.05$) (**Figures 3C,D**). The damage on intestinal mucosa by visual inspection in the DSS group presented significantly higher congestion and edema, more serious erosion or intestinal adhesion, bigger ulcers, and higher CDMI score ($p < 0.01$) (**Figure 3E**) compared with the OC-B-BBR group. Similarly, the inflammatory cell infiltration and histological score of H&E staining sections of colon tissue in the DSS group were significantly higher compared with the OC-B-BBR group ($p < 0.01$) (**Figures 3F,G**). There were no significant differences between the OC-B-BBR and mesalazine group in the DAI, colon length, spleen index, or CMDI score. The histological scores of the OC-B-BBR group were significantly lower than that of the mesalazine group ($p < 0.05$). Above all, OC-B-BBR could effectively ameliorate DSS-induced colitis in mice and may have potential advantages over mesalazine.

OC-B-BBR Suppressed the Secretion of Some Inflammatory Cytokines in DSS-Induced Mice

Excessive production of proinflammatory cytokines lead to the progression and exacerbation of colitis. To understand the anti-inflammatory effect of OC-B-BBR, we measured the levels of proinflammatory cytokines in the colon homogenates by ELISA. The results showed that the levels of TNF-α and IL-6 were significantly increased after DSS-induced ($p < 0.05$ or $p < 0.01$). The increase of IL-6 was significantly reduced by OC-B-BBR treatment ($p < 0.01$), while the increase of TNF-α was significantly reduced by mesalazine treatment ($p < 0.05$). There were no significant differences of TGF-β and IL-23 in the four groups (**Figures 3H–K**).

OC-B-BBR Modified Gut Microbiota

α-diversity analysis reflected the richness and diversity of microbial communities, including a series of statistical analysis indexes. The Chao and ACE indexes are used to estimate the microbial richness, while Shannon index is used to estimate the microbial diversity. The ACE index of DSS group was significantly lower than that of the normal group, of which the OC-B-BBR group and mesalazine group were significantly increased ($p < 0.05$) (**Figure 4A**). Although the Chao index did not increase significantly, the increase in species richness was demonstrated to some extent (**Figure 4A**). Shannon index showed no significant difference among the four groups (**Figure 4A**). No apparent clustering was observed in principal component analysis (PCA) (**Figure 4B**) or principal coordinate analysis (PCoA) (**Figure 4B**) among the normal group, DSS group, OC-B-BBR group, or mesalazine group.

At phylum level, the compositions of gut microbiota in each group were shown in **Figure 4C**. Compared with the normal group, the relative abundance of Bacteroidetes, Deferribacteres, and Proteobacteria in the DSS group increased significantly, while the relative abundance of Firmicutes and Verrucomicrobia decreased significantly ($p < 0.05$ or $p < 0.01$) (**Figures 4D,E**). Compared with the DSS group, the relative abundance of Firmicutes increased significantly in the OC-B-BBR group, while the relative abundance of Proteobacteria decreased ($p < 0.05$) (**Figure 4F**). There was no significant difference between the DSS group and mesalazine group (**Figure 4G**).

At genus level, the compositions of gut microbiota in each group were shown in **Figure 4H**. Compared with the normal group, the relative abundance of *Bacteroides*, *Escherichia*, *Helicobacter*, and so on increased significantly in the DSS group, while the relative abundance of Akkermansia and Coprococcus decreased significantly ($p < 0.05$ or $p < 0.01$) (**Figure 4I**). Compared with DSS group, the relative abundance of *Bacteroides* and *Escherichia* decreased significantly in the OC-B-BBR group ($p < 0.05$) (**Figure 4J**). There was no significant difference between the DSS group and mesalazine group (**Figure 4K**).

LEfSe linear discriminant analysis (LDA) was used to discriminate the significant different species (LDA>4, $p < 0.05$). The higher the LDA score, the greater effect of the

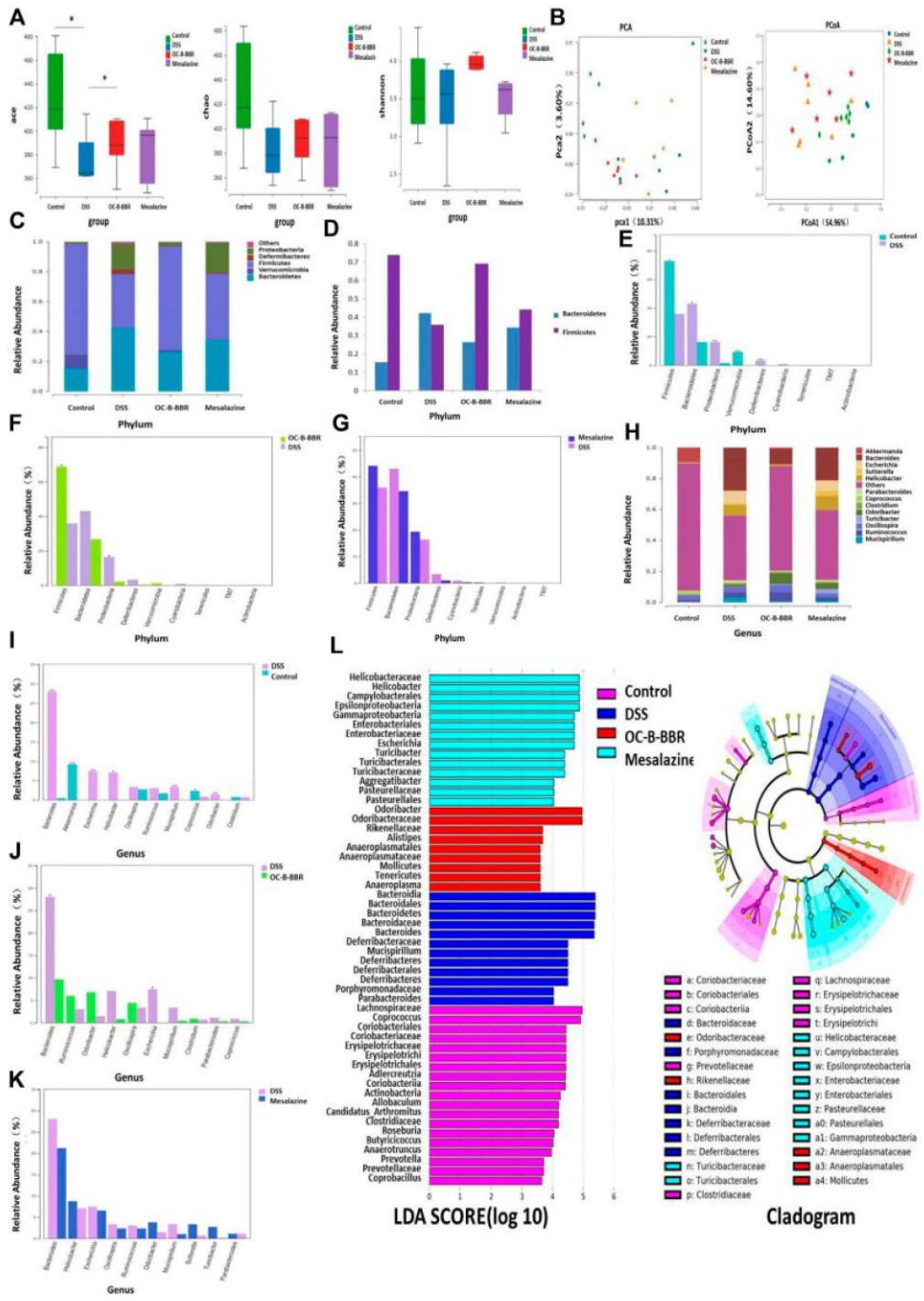

FIGURE 4 | (A) α-Diversity estimated by ACE, Chao, and Shannon indexs,*$p < 0.05$; **(B)** PCA score and PCoA score plots; **(C)** Gut microbiota composition at phylum level in each group; **(D)** Firmicutes/Bacteroidetes ratio at phylum level in each group; **(E)** The proportions of key species at phylum level, Normal group vs DSS group; **(F)** The proportions of key species at phylum level, OC-B-BBR group vs DSS group; **(G)** The proportions of key species at phylum level, Mesalazine group vs DSS group; **(H)** Gut microbiota composition at genus level in each group; **(I)** The proportions of key species at genus level, Normal group vs DSS group; **(J)** The proportions of key species at genus level, OC-B-BBR group vs DSS group; **(K)** The proportions of key species at genus level, Mesalazine group vs DSS group; **(L)** LDA score and LEfSe taxonomic cladogram.

relative abundance of species on the difference. There were significant differences in the composition of key species among the four groups. A LEfSe taxonomic cladogram represented key bacterial alterations. Different colors of purple, blue, red, and green respectively represent the NC, model, OC-B-BBR, and mesalazine groups. Each small circle at different taxonomic levels represents a taxon at that level, and the diameter of the small circle is proportional to the relative abundance (**Figure 4L**).

DISCUSSION

Chinese herbal medicine treatment of inflammatory bowel disease has a long history in China and around the world (Zhao et al., 2017). However, due to the low content of active ingredients and oral bioavailability, the further improvement of the curative effect of Chinese herbal medicine is limited. The development of targeted drug delivery based on nano technology presents a new approach for natural drugs extracted from Chinese herbal medicine in the treatment of IBD.

Chitosan is a natural polymer of living organisms, which provides a basis for the construction of functional polymer biomaterials with biological properties and unique physicochemical properties, biocompatibility, and biodegradability. In particular, through the controlled functionalization of some simple borate parts, we can obtain an intelligent system for specific site drug delivery with certain required response characteristics, such as ROS response (Maji et al., 2015). Herein, based on ROS responsiveness, we designed a new type of chitosan nanocarrier to achieve targeted drug delivery to inflammation sites. The ROS responsive group, which can effectively deliver the encapsulated BBR to the inflammatory site by ROS-triggered release in the microenvironment of oxidative stress, was formed by the self-assembly of amphiphilic carboxymethyl chitosan and phenylborate side groups. The selectivity of phenylborate as the linker was mainly due to its ROS responsiveness and biocompatibility, as well as convenient conjugation with drugs *via* catechol moiety. Many natural anti-inflammatory drugs contained catechol, such as quercetin and rutin. Thus, the current design provided a realistic and general strategy for constructing catechol-based responsive nanodrug delivery system.

Dynamic light scattering (DLS) was used to evaluate the size and polydispersity index (PDI) of the OC-B-BBR micelles. The hydrodynamic average size was about 220 nm, with a relatively similar particle size distribution of 0.22 (**Table 1**). However, in the case of the empty nanocarrier OC-B, the detected particle size distribution was slightly wider at 0.42, due to the weak hydrophobicity in the core without drugs. This result was consistent with the observation on SEM. In the subsequent stability tests, the relatively intact micelles were obtained in a few days by DLS and zeta potential analysis, which provided a vital guarantee for stable drug delivery before reaching the inflammatory site.

Here our results showed that OC-B-BBR alleviated DSS-induced colitis in mice. Compared with the DSS group, after OC-B-BBR treatment the DAI score and spleen index was decreased, the colon length was increased, and the damage to the colon (congestion, edema, erosion, ulcer or inflammatory cell infiltration etc) was reversed. A particular concern was that histological scores were significantly lower in the OC-B-BBR group than in the mesalazine group, while there were no significant differences between the two groups on other indicators. This showed that for histological healing OC-B-BBR may have had potential advantages over mesalazine. Histological deep healing is the highest goal of clinical treatment for IBD patients. A recent systematic review and meta-analysis revealed that patients who achieved endoscopic and histological remission have a significantly lower risk of clinical relapse than patients who achieved clinical remission (Yoon et al., 2020). The proinflammatory cytokines levels correlate with the severity of colitis. Our results showed that OC-B-BBR treatment inhibited the release of IL-6, while mesalazine treatment inhibited the release of TNF-α. It suggests that OC-B-BBR and mesalazine may exert anti-inflammatory effects through different pathways.

The pathogenesis of IBD is complicated and not clear. It is now accepted that a complex interplay of genetic and environmental factors and gut microbiota lead to abnormal immune responses and chronic colitis (Nishida et al., 2018). Compared with healthy people, IBD patients had less bacteria with anti-inflammatory capacities and more bacteria with inflammatory capacities (Peterson et al., 2008). The most recognized changes were a decrease in the diversity of the intestinal microbial community, a decrease in abundance of Firmicutes, and increases in abundance of Proteobacteria and Bacteroidetes (Manichanh et al., 2006; Walker et al., 2011). Our results showed that OC-B-BBR increased the community richness of gut microbiota decreased by DSS induction. At phylum and genus level, compared with the DSS group, the relative abundance of Firmicutes was increased, while the relative abundance of Proteobacteria, *Bacteroides*, and *Escherichia* was decreased in the OC-B-BBR group. In the DSS group, the ratio of Firmicutes and Bacteroidetes was inverted, and OC-B-BBR treatment was shown to restore its normal trend. OC-B-BBR treatment shifted the microbiome toward a "healthy" phenotype. The relative abundance of species in the mesalazine group were not significantly different from the DSS group. OC-B-BBR may attenuate DSS-induced colitis by modulating the composition of bacterial communities. In future studies, we need to explore the mechanism of OC-B-BBR inhibiting inflammation by regulating gut microbiota.

CONCLUSIONS

In summary, BBR was conjugated to carboxylmethyl chitosan by aryl boronic ester, giving a potential ROS responsive for an effective delivery of drugs to the inflammatory tissue. OC-B-BBR as carboxylmethyl chitosan nanomicelles were prepared and characterized, which ameliorates DSS-induced colitis and remodels gut microbiota. The novel natural drug nano delivery system may represent a promising approach for improving IBD treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The animal study was reviewed and approved by the Animal Care and Use Committee of Beijing Hospital of traditional Chinese Medicine, Capital Medical University.

AUTHOR CONTRIBUTIONS

LZ, SZ, and CL conceived and designed the experiments. XD, XK, and YL performed the experiments. XD, JT, and WD contributed to the data analysis. LZ guided the animal experiment work. LZ and JT wrote the article and DL assisted in this work. SZ and CL drafted and revised the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.644387/full#supplementary-material.

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Review Article

REVIEW ARTICLE

Role of gut microbiota in functional constipation

Shengsheng Zhang[1], Ruixin Wang[1], Danyan Li[1], Luqing Zhao[1,*] and Lixin Zhu[2,*]

[1]Digestive Disease Center, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, P. R. China; and [2]Department of Colorectal Surgery, Guangdong Institute of Gastroenterology, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, P. R. China

*Corresponding author. Guangdong Institute of Gastroenterology, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, Department of Colorectal Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou, Guangdong 510655, P. R. China. Tel: +86-19946256235; Email: zhulx6@mail.sysu.edu.cn and Digestive Disease Center, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, 23 Meishuguan Back Street, Beijing 100010, P. R. China. Tel: +86-15101019831; Fax: +86-10-52176720; Email: zhaoluqing@bjzhongyi.com

Abstract

Functional constipation (FC) is common, yet the etiology is not clear. Accumulating evidence suggests an association between FC and abnormal gut microbiota. The relationship between the gut microbiota and the gut transit is likely bidirectional. This review summarizes the current evidence regarding the impact of gut microbiota on the pathogenesis of FC. By modulating the colonic motility, secretion, and absorption, gut microbiota may contribute to the development of FC through microbial metabolic activities involving bile acids, short-chain fatty acids, 5-hydroxytryptamine, and methane. In support of the key roles of the gut microbiota in FC, treatment with probiotics, prebiotics, synbiotics, and traditional Chinese medicine often result in compositional and functional changes in the gut microbiota. Further studies on the pathogenesis of FC and the therapeutic mechanism of microecological agents will provide a knowledge base for better management of FC.

Key words: gut microbiota; functional constipation; bile acids; SCFA; serotonin; traditional Chinese medicine

Introduction

Functional constipation (FC) refers to constipation without an organic etiology [1, 2]. Patients with FC have symptoms of predominantly difficult, infrequent, or a feeling of incomplete defecation, which may be accompanied by abdominal pain and bloating. FC has a significant impact on patients' quality of life. According to the Rome IV criteria, to diagnose FC [3] (Figure 1), the patient must have one of the following conditions for more than 6 months and have two or more of the following conditions within the last 3 months: (i) sensation of straining during >25% of defecations, (ii) lumpy or hard stools of >25% of defecations (Bristol stool type 1 and 2) [4], (iii) sensation of incomplete evacuation during >25% of defecations, (iv) sensation of anorectal obstruction/blockage during >25% of defecations, (v) manual maneuvers for >25% of defecations, and (vi) fewer than three spontaneous bowel movements per week. In addition, diagnosis of FC should meet the requirement that loose stools are rarely present without using laxatives and that irritable bowel syndrome (IBS) is not diagnosed at the same time.

A recent demographic survey of 6,300 cases from three countries showed that the prevalence of FC was 6.9% (95% confidence interval [CI], 5.8%–8.0%) in the USA, 7.9% (95% CI, 6.7%–9.1%) in Canada and 8.6% (95% CI, 7.4%–9.9%) in the UK, according to the Rome IV criteria [5]. Globally, the prevalence of FC

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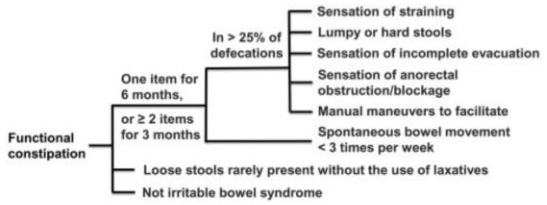

Figure 1. Diagnosis of functional constipation according to the Rome IV criteria.

from 1947 to 2010 was 14% (95% CI, 12.0%–17.0%) according to the Rome I, II, III criteria or another informal diagnostic standard. South Asia and East Asia had the lowest prevalence of 11% (95% CI, 7.0%–15.0%), while South America had the highest prevalence of 18% (95% CI, 15.0%–22.0%). Caution needs to be exercised in comparing the incidences of FC in different countries since the diagnosis criteria and the methods for data collection may differ among studies. FC is positively associated with age and more frequently occurs in people who are >60 years old [6]. The pathophysiology of FC remains unknown, but it is generally considered to be multifactorial. Recognized pathophysiological factors include genetic traits; lifestyle including diet, fluid intake, physical activity; colonic dismotility; psychological factors such as anxiety and depression; and the gut microbiota, which is the main focus of this review. Traditionally, three types of FC have been recognized: normal-transit constipation (NTC), slow-transit constipation (STC) and rectal-evacuation disorders [7]. The majority of FC patients have NTC (65%), followed by evacuation disorder (30%) and STC (5%) [8].

The first choices for FC treatment are nonpharmacological interventions including education on toileting posture and behavior, dietary recommendations, and regular physical activity [9]. Ohlsson and Manjer [10] showed that the lack of exercise and regular diet habit are independent risk factors for gastrointestinal symptoms in patients with functional gastrointestinal diseases. Traditional pharmacological treatments include osmotic laxatives and stimulant laxatives. Polyethylene glycol (PEG), the most frequently used osmotic laxative for FC, increases fecal volume and promotes intestinal peristalsis. Many studies have shown that PEG increases the frequency of defecation and has fewer side effects [11]. Therefore, PEG can be used as a long-term first-line treatment. In contrast, although stimulant laxatives can make a fast improvement in stool consistency and frequency, they should not be used for >4 weeks considering the possible adverse effects [12]. New therapeutic agents, including prosecretory agents (e.g. linaclotide), serotonergic agents (e.g. 5-hydroxytryptamine 4 agonist), cholinesterase inhibitors (e.g. pyridostigmine), and bile-acid (BA) regulators (e.g. elobixibat) etc. may improve FC symptoms by promoting colon secretion and enhancing gastrointestinal motility [9]. Other treatment options with evidence for efficacy include biofeedback therapy [13], transanal irrigation [14], surgical interventions [15, 16], and neuromodulation [14]. Despite all these intervention options, 40% of pediatric [17] and more than half of adult FC patients [18–20] are dissatisfied with the treatments due to the lack of efficacy and adverse effects. Therefore, new management strategies have been explored. One of the possible intervention targets is the gut microbiome, which was supported by the observation that interventions with probiotics, prebiotics, and fecal-microbiota transplantation improved colonic transit and defecation frequency [21–23]. Herein, we summarize the current knowledge on the potential contribution of the gut microbiota in the pathogenesis of FC.

Intestinal flora characteristics of patients with FC

Zoppi *et al.* [24] pioneered the study of the gut microbiota in FC using culture-based microbiological methods in 1998. They reported that constipation in children was associated with increased abundance in clostridia and bifidobacteria in the gut compared to healthy controls. Later, Khalif *et al.* [25] conducted a similar study with adult patients, still using culture-based microbiological methods, and reported that the abundances of *Bifidobacterium* and *Lactobacillus* were lower in constipated patients than in the controls. The opposite observations regarding the abundance of bifidobacteria may be explained by the pathophysiological differences between pediatric and adult patients. It is also important to note that culture-based methods tend to cause inaccurate observations in microbiota study because: (i) many species are not cultured, (ii) strict anaerobes die in an oxygenated environment and therefore tend to be underestimated, and (iii) *in vitro* culture changes the original structure of the microbiota.

In around 2015, Kim *et al.* [26] studied the microbiota of FC using a culture-independent method: the quantitative real-time polymerase chain reaction method. They reported that *Bifidobacterium* and *Bacteroides* species were decreased in the feces of FC. Although the methodology that Kim *et al.* [26] used is one large step more advanced than those reported in most studies on this topic, we have now progressed to the era of high-throughput sequencing and we conducted the first 16S rRNA sequencing study of the gut microbiota with adolescent FC patients [27]. Because we excluded those patients treated with antibiotics or proton-pump inhibitors, which are known to impact the gut microbiota, we were able to identify significant changes in the gut microbial composition of FC at every taxonomic level, with a relatively small sample size. At the genus level, the microbiota of FC exhibited a decreased abundance of *Prevotella* and increased abundance of *Coprococcus*, *Ruminococcus*, *Blautia*, *Anaerotruncus*, and *Clostridium*. *Prevotella* encodes a large set of enzymes for fiber metabolism [28] and is known for its association with dietary fibers [29]. Therefore, the decreased abundance of *Prevotella* in FC is consistent with the observation that FC patients usually have a low-fiber diet [30, 31]. In contrast to the findings of previous studies, conventional probiotic genera *Lactobacillus* and *Bifidobacterium* exhibited a trend for increased abundance in FC. At the community level, increased species richness was observed in the gut of FC, likely because of the prolonged incubation time of the gut microbiota in the presence of FC.

Recently, Mancabelli *et al.* [32] examined the gut microbial composition of adult FC patients using both the 16S rRNA sequencing and the whole-genome sequencing methods. Their 16S rRNA sequencing data indicated that the gut microbiota of FC patients was depleted of *Bacteroides*, *Roseburia*, and *Coprococcus 3*, which would predict a decreased level of short-chain fatty acid (SCFA) production. However, their whole-genome sequencing data did not validate this functional change.

Apparently, at this time, there is no consensus on the gut microbial structure characteristic of FC patients. Inconsistent observations may have been the consequences of the cultural and demographical differences of the study cohorts, different analysis techniques, and possible evolution of the disease over

time. Table 1 summarizes several typical studies on the structural change in the gut microbiota in patients with FC.

The relationship between the gut microbiota and the gut transit is likely bidirectional. Prolonged colonic transit in FC may facilitate the amplification and colonization of slow-growing species, leading to profound structural and functional alterations of the entire microecology. On the other hand, environmental factors may cause alterations in the gut microbiota, which, in turn, may contribute to the pathogenesis of FC through microbial metabolic activities.

The contribution of intestinal flora in the pathophysiological mechanism of FC

The current hypothesis is that the gut microbiota contributes to the pathogenesis of FC. This was supported by the observations that many risk factors of FC including age, diet, obesity, and stress have a large impact on the gut microbiota [33–35]. Thus, it is speculated that these risk factors may cause FC through mechanisms involving altered gut microbiota. The underlying mechanisms are the focus of the current review (Figure 2).

Mechanisms involving BAs

Primary BAs are initially produced in the liver. Normally, most BAs are reabsorbed into the small intestine while ~5% may arrive at the colon, where primary BAs are deconjugated and modified into secondary BAs by the gut microbiota [36, 37].

BAs may participate in the pathophysiology of FC through their effect on intestinal motility and colonic fluid transport. BAs are known to stimulate the release of 5-hydroxytryptamine (5-HT) and calcitonin gene-related peptide from enterochromaffin cells and intrinsic primary afferent neurons by activating the G protein-coupled BA receptor (TGR5), leading to the bowel peristaltic reflex [38, 39]. Several studies on FC patients treated with an ileal BA transporter inhibitor (elobixibat) demonstrated a causal relationship between elevated BA level and improved colonic transit [40–43].

There are direct and indirect mechanisms for BAs to stimulate fluid transport. BAs stimulate Cl^- secretion and inhibit Na^+ absorption from colonic epithelial cells through regulation of the ion pumps, exchangers, and transporters [44]. In addition, BAs may indirectly stimulate colonic secretion through their effect on local neurons [45] and immune cells [46].

Animal studies suggest that it is the deconjugated BAs that impact colonic transit. BAs are conjugated with glycine or taurine before being secreted from hepatocytes. After arriving at the colon, BAs are deconjugated by bacterial bile salt hydrolase before further modification. Microbial transplantation studies in mice indicated that altered microbiota affects gastrointestinal transit, through its impact on BA deconjugation [47, 48]. It is noteworthy that the microbial metabolisms of BAs are different between mice and humans, thus the mice studies remain to be validated in humans.

Several mechanisms have been proposed to explain how BAs mediate the microbial effects on FC. First, the gut microbiota may affect gastrointestinal transit through its regulation of BA synthesis. The gut microbiota is equipped with enzymes for the production of secondary BAs, which may suppress the FGF19- and FXR-mediated signaling, leading to the induction of CYP7A1 [49, 50], and consequently elevated *de novo* BA synthesis and improved colonic transit. To test this hypothesis, an integrated study on the colonic BA profiles, the abundances of BA

Table 1. Structural changes in gut microbiota in functional constipation

Reference	Year	Methods	Inclusion criteria	Patients	Controls	Outcomes
Zoppi *et al.* [24]	1998	Microbial culture	Stool frequency less than one per 48 h and hard stool consistency	Children ($n = 28$, mean age 9.5 years)	Children ($n = 14$, mean age 7.9 years)	*Bifidobacteria*↑* *Lactobacilli*↑ *Bacteroides*↑ *Clostridia*↑*
Khalif *et al.* [25]	2005	Microbial culture	Rome II	Adults ($n = 57$, mean age 42.2 years)	Adults ($n = 25$)	*Bifidobacterium*↓* *Lactobacillus*↓ *Bacteroides*↓ *Clostridium*↓
Kim *et al.* [26]	2015	qRT-PCR	Rome III	Adults ($n = 30$, mean age 35 years)	Adults ($n = 30$, mean age 32 years)	*Bifidobacterium*↓* *Lactobacillus*↓ *Bacteroides*↓* *Clostridium*↓
Zhu *et al.* [27]	2014	16S rRNA	Clinical practice guideline developed by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition	Children ($n = 8$, mean age 11.8 years)	Children ($n = 14$, mean age 13.2 years)	*Prevotella*↓* *Coprococcus*↑* *Ruminococcus*↑* *Blautia*↑* *Anaerotruncus*↑* *Clostridium*↑*
Mancabelli *et al.* [32]	2017	16S rRNA and shotgun metagenomics	Rome III	Adults ($n = 68$, mean age 44 years)	Adults ($n = 44$, mean age 39 years)	*Bacteroides*↓* *Roseburia*↓* *Coprococcus 3*↓* Faecalibacterium↑*

*$P < 0.05$.

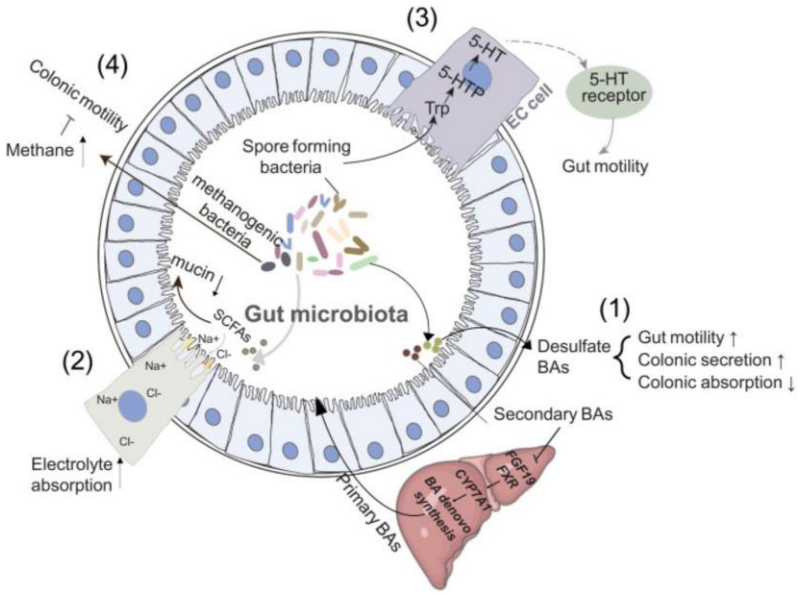

Figure 2. Potential molecular mechanisms for the gut microbiota that contribute to the pathogenesis of functional constipation (FC). (1) Bile acids (BAs) stimulate bowel movement and colonic secretion and suppress colonic absorption. The gut microbiota impacts these processes by regulating the BA levels, as well as the sulfation of BAs, which abolishes the effects of BAs on colonic transit. (2) Elevated levels of short-chain fatty acids (SCFAs), the major group of microbial fermentation products, stimulate electrolyte absorption and suppress mucin secretion, thus contributing to the pathogenesis of FC. The effect of SCFA on colonic motility is a controversial topic. (3) 5-hydroxytryptamine (5-HT) stimulates colonic motility. The gut microbiota regulates the level of 5-HT through several mechanisms and thereby affects the pathogenesis of FC. (4) Methane produced by the gut microbiota reduces bowel movement. 5-HTP, 5-hydroxytryptophan.

metabolizing bacteria, and the cell biology of the colonic epithelium is required.

Another mechanism for the gut microbiota to influence FC is through its impact on BA sulfation, which abolishes the effect of the BAs on fluid transport [51, 52]. BA sulfation likely occurred in hepatocytes, while colonic bacterial bile salt sulfatase may desulfate BA, empowering its effect to stimulate colonic secretion and transit, and consequently improve colonic fluid transport [53]. Future study may characterize the abundances of sulfated BAs in the gut of patients with FC and its association with sulfatase-encoding bacteria.

Mechanisms involving SCFAs

SCFAs including acetate, propionate, and butyrate are the major fermentation products of the gut microbiota. Elevated levels of SCFAs are found in the stools of FC patients. Jalanka *et al.* [54] reported that the level of fecal acetate in FC patients was 2.2-fold higher than that in healthy controls, and that the levels of acetate, butyrate, and propionate were associated with the transit time in constipated patients. Iso-butyrate levels were also significantly higher in FC subjects than in healthy subjects [55].

SCFAs may contribute to the pathogenesis of FC by regulating colonic electrolyte absorption and secretion. SCFAs, especially butyrate, stimulate electrolyte absorption. The stimulation of Na^+ and Cl^- absorption by mucosal butyrate was greater than that by propionate and acetate [56]. The effect of butyrate on mucin secretion takes a biphasic mode: butyrate stimulation of mucin section peaks at 5 mM of butyrate. At concentrations of >5 mM, butyrate is inversely correlated with mucin section [57]. These results consistently support the roles of elevated SCFAs in increased electrolyte absorption and decreased mucin secretion. On the other hand, the effect of SCFAs on colonic motility is controversial. In some studies, SCFAs increased colonic motility in rats [58, 59], whereas other studies reported opposite observations [60, 61]. Several gaps and pitfalls are to be addressed to understand the role of SCFAs in FC. First, SCFAs measured in the published studies represent what were not absorbed, whereas the relevant SCFAs are those in contact with the SCFA receptors. Second, the working concentrations in different species likely vary and caution is needed when interpreting observations made in studies using SCFA concentrations that are far higher than physiological concentrations. Third, the long-term effects of SCFAs on the neural structure are important and need to be considered when interpreting the SCFA effects on colonic secretion, absorption, and motility [59].

Studies on the structure of the gut microbiota seem to support a role for SCFAs in the pathogenesis of FC. Butyrate-producing genera, *Roseburia* and *Faecalibacterium*, were increased in adolescent FC according to 16S rRNA sequencing studies [27, 62]. In a similar 16S rRNA sequencing study for adult FC patients, Mancabelli *et al.* [32] reported that *Faecalibacterium* is elevated in FC. However, their data indicated that other butyrate-producing bacteria *Roseburia* and *Coprococcus 3* were depleted in FC. Shotgun metagenomic sequencing by Mancabelli *et al.* [32] does not support altered SCFA production in FC, which may be explained by very small sample size. Further study integrating microbiome survey, metabolome analysis, colonic absorption, secretion, and colonic motility is warranted to understand the role of the gut microbiota in promoting FC through altered SCFA production.

Mechanisms involving 5-HT

Produced by enterochromaffin cells, 5-HT is an abundant neurotransmitter in the enteric nervous system. Although it is a

controversial subject, a significant amount of evidence suggests that 5-HT stimulates colonic motility through its receptors 5-HT3 and 5-HT4 [63]. For example, prucalopride, a highly selective agonist for serotonin 5-HT4 receptor, increases the number of bowel movements per week in adults with chronic FC [64]. Thus, the gut microbiota may impact the gut motility by regulating the production of 5-HT. Theoretically, the gut microbiota may regulate the production of 5-HT via several mechanisms. First, the gut microbiota influences the growth of colon enterochromaffin cells, suggested by the upregulation of 5-HT–positive enterochromaffin cells in germ-free rats [65]. In contrast to that of rats, the gut microbiota of mice and humans seem to have an opposite effect on 5-HT production. Mediated by microbial metabolites, indigenous spore-forming bacteria (Sp) from the mouse and human microbiota promote 5-HT biosynthesis from colonic ECs [66]. Independent studies have suggested that microbial metabolites BAs and SCFAs may induce the release of 5-HT from enterochromaffin cells [38, 39, 67].

A recent study suggests a different mechanism. Cao *et al.* [68] reported that the gut microbiota of FC patients upregulates the expression of serotonin transporter, which removes 5-HT from the gut. This causes decreased colonic transit and FC. It is noteworthy that the authors stated several times that they performed a 16S pyrosequencing study, but provided a description of illumina Miseq sequencing in the method section [68].

Finally, the gut microbiota may influence 5-HT production by regulating tryptophan metabolism in the gut [69]. For example, the gut microbiota may upregulate the production of indole and kynurenine from tryptophan, thereby reducing the substrate for the production of 5-HT and consequently leading to FC.

A fundamental gap in the study of 5-HT in FC is whether mucosal 5-HT is altered in FC patients. While some studies reported decreased 5-HT [64, 70], there were reports that the 5-HT level was not altered [71] or was increased in FC [72]. Vigorous studies are needed to validate the role of 5-HT in mediating the effect of gut microbiota on the pathogenesis of FC.

Mechanisms involving methane

It has long been proposed that methanogenic gut microbiota causes constipation by reducing bowel movements [73]. The hypothesis has been supported by the observations that FC patients carry gut microbiota enriched with methanogenic bacteria [74, 75]. In line with this, in patients with constipation-predominant IBS, treatment with antibiotics reduced the methanogenic bacteria in the gut microbiota and led to improved symptoms [76]. However, it is worth noting that no control was used in this retrospective study. On the other hand, one study reported that in patients with FC, methane production was associated with the gut microbial composition, but not with constipation or colonic transit [77]. Caution is also required to interpret these data as all of the 25 patients with constipation included 13 FC, 6 IBS with constipation, and 6 mixed IBS. Intervention studies with more strict inclusion criteria and a larger sample size are needed to clarify the role of methanogenic bacteria in FC.

FC treatments targeting the gut microbiota

In support of the roles of the gut microbiota in the pathogenesis of FC, various microbial interventions including probiotics, prebiotics, synbiotics, and traditional Chinese medicine (TCM) have shown beneficial effects on FC. In addition, some of the intervention studies support the mechanisms discussed above.

Probiotics

Probiotics, the most widely used microecologics, are effective in treating a wide variety of diseases by regulating the immune response, preventing the colonization of pathogens, improving gut barrier function, and reducing stress and anxiety, etc. [78]. Although individual studies have reported varied efficacies [79, 80], an earlier systemic review and meta-analysis of randomized–controlled trials indicated that probiotics may improve the whole-gut transit time, stool frequency, and stool consistency; *Bifidobacterium lactis* showed better efficacies than *Lactobacillus casei Shirota* [81]. A more recent systemic review and meta-analysis arrived at a similar conclusion that probiotics increase stool frequency and decrease intestinal transit time in FC patients [82]. Most recently, a meta-analysis of randomized–controlled trials of probiotics on FC concluded that probiotics consisting of multispecies, not single species such as *B. lactis* or *B. longum* alone, significantly reduced the whole-gut transit time, increased the defecation frequency, improved stool consistency, and decreased bloating [83]. It is worth noting that probiotics are likely to have a greater effect on the small bowel than on the colon, as the small bowel has far fewer competing bacteria. One study showed that probiotics reduced both the small-bowel transit time and the colonic transit time [84]. It is possible that the shortened small-bowel transit would increase the inflow to the colon and would consequently accelerate colonic transit.

However, similar studies with pediatric patients do not support the efficacy of probiotics on pediatric FC [85, 86]. The difference between adult and pediatric patients with FC in response to probiotics may be related to different microbial compositions in adult and pediatric subjects: while adult patients with FC exhibited a decreased abundance of *Bifidobacterium* [26], adolescent patients with FC exhibited a trend for elevated abundance of *Bifidobacterium* and *Lactobacillus* [27].

To explore the different effects of probiotic strains in FC, Wang *et al.* [87] treated constipated mice with *B. longum*, *B. infantis*, *B. animalis*, *B. bifidum*, *B. adolescentis*, and *B. breve*, respectively. They observed that *B. longum*, *B. infantis*, and *B. bifidum* were the most effective strains to relieve constipation. The improved symptoms were attributed to increased abundance of *Lactobacillus* and reduced levels of pathogenic bacteria (*Alistipes*, *Odoribacter*, and *Clostridium*). It is important to note that a randomized, double-blind, placebo-controlled probiotics treatment trial on FC is rare. In one of these trials, Ibarra *et al.* [88] reported no difference between probiotics and the placebo in primary analysis, but in a post hoc analysis, they reported that *B. animalis subsp. lactis* HN019 (HN019) increased the frequency of spontaneous defecations and reduced the degree of straining in FC patients.

Prebiotics

Prebiotics refers to non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon [89]. Recently, a randomized placebo-controlled trial of prebiotics for the treatment of FC was reported. UG1601, composed of inulin, lactitol, and aloe vera gel, was used to treat female patients with mild chronic FC [90]. Although UG1601 seemed to be more effective than placebo in improving abdominal and

fecal symptoms, statistical significance was not achieved. Other interesting observations include reduced levels of serum cluster of differentiation 14 (CD14) and lipopolysaccharide (LPS), and increased abundance of *Roseburia hominis*, a butyrate-producing bacterium, upon UG1601 treatment.

D-tagatose is a monosaccharide often used as a food supplement. Liang *et al.* [91] found that high-dose d-tagatose restored the gastrointestinal transit rate of constipated mice induced by loperamide to a similar level of that of control mice, and improved the overall defecation condition including fecal weight, fecal number, and time to the first black-stool defecation. These therapeutic effects were attributed to the increased levels of excitatory neurotransmitters (Ach and SP) and the reduced level of inhibitory neurotransmitters (NO). The therapeutic mechanisms of d-tagatose may also involve the gut microbiota as the prebiotic therapy restored the composition of the intestinal flora.

Similarly, partially hydrolysed guar gum (HHGG), a fiber supplement, was shown to increase the fecal water content and enhance the small-intestinal transit of loperamide-induced constipated mice [92]. The therapeutic effects may be mediated by the gut microbiota as the prebiotics caused significant changes in the gut microbiota and elevated production of SCFAs.

Another popular prebiotics, β-glucan, is a polysaccharide widely found in yeast, fungus, and plants. Chen *et al.* [93] used the β-glucan extracted from bread yeast cells to treat loperamide-induced constipated mice and found enhanced intestinal motility. The pharmacological effect of β-glucan may be mediated by the enhanced expression of epithelial tight junction proteins (zonula occludens-1 and mucin-2) and neurotransmitters (acetylcholinesterase and serotonin). The gut microbiota was likely involved in the therapeutic effect of β-glucan as it restored the intestinal flora of the constipated mice toward a normal composition.

Although efficacies were shown with the loperamide-induced mice model, these prebiotics remain to be validated in randomized, double-blind, placebo-controlled trials.

Synbiotics

Synbiotics are combinations of probiotics and prebiotics, which may exhibit synergistic effects of both components [94]. In a pilot randomized, double-blind, controlled trial of a small sample size, synbiotic supplement Psyllogel Megafermenti improved defecation and decreased ITT [95]. However, in another randomized, double-blind, placebo-controlled trial with a larger sample size, no significant effect was found for a synbiotic composed of *B. lactis* BB12, *L. plantarum* LP01, and inulin-oligofructose [96]. A more recent trial using a combination of polydextrose and *L. helveticus* found beneficial effects on intestinal transit and fecal pH, but no significant advantage was found with this synbiotic compared with *L. helveticus* alone [97]. Perhaps different types of synbiotics have different therapeutic efficacies on FC. More clinical trials are needed to identify effective synbiotics and to confirm the therapeutic effects.

TCM

Several TCM herbs and formulations are effective for FC. The hemp seed soft capsule (HSSC) was developed from the ancient traditional prescription 'hemp seed pill', which consists of *Semen Cannabis*, *Magnolia officinalis*, *Fructus Aurantii Immaturus*, *Radix Paeoniae Alba*, *Almond*, and *Rheum rhabarbarum*. As a representative prescription of TCM in the treatment of constipation [98], the hemp seed pill has been known to improve colonic secretion and transit [99]. With loperamide-induced constipated rats, Lu *et al.* [100] showed that HSSC increased the fecal wet weight and water content, which was attributed to the combined actions of cAMP-dependent and Ca^{2+}-dependent Cl^- channels, NKCC, Na^+-$HCO3^-$ co-transporter, or Cl^-/$HCO3^-$ exchanger.

Recently, the gut microbiota has been often reported to participate in the therapeutic effects of these herbs and formulations. Invented in the Qing Dynasty ~300 years ago, Zengye decoction (ZYD) has been used to cure 'dryness' by promoting the production of body fluids according to TCM theory. Liu *et al.* [101] examined the effect of ZYD on the gut microbiota of constipated rats. They found that ZYD restored the composition of the gut microbiota toward a normal state by reducing the abundance of *Helicobacteraceae*, *Desulfovibrionaceae*, *Ruminococcaceae*, *Lactobacillaceae*, *Prevotellaceae*, and *Dorea*, while increasing the abundance of *Aeromonadaceae*, *Oxalobacteraceae*, *Veillonellaceae*, *Clostridiaceae*, and *Roseburia*. Metabolomic analysis revealed that ZYD caused microbial changes in the metabolism of energy, amino acids, methane, and glutathione.

Records of mulberry fruit for the treatment of constipation and other digestive diseases date back to 200 BC. According to TCM theory, mulberry fruit can be used to treat 'yin' deficiency. Hu *et al.* [102] used the mulberry fruit to treat diphenoxylate-induced constipated mice and found that the treatment increased the fecal water content, shortened the first red-stool defecation time, and increased the gastric-intestinal transit rate. The mulberry-fruit treatment caused alterations in the gut microbiota, with increased abundance of *Lactobacillus*, *Bifidobacterium*, and *Eubacterium*, and decreased abundance of *Helicobacter*, *Alloprevotella*, and *Prevotellaceae*. The compositional change in the microbiota was accompanied by decreased expression of aquaporin genes (Aqp3, Aqp4, Aqp8, and AqP9), reduced levels of inhibitory neurotransmitters, and increased levels of excitatory neurotransmitters and SCFAs, suggesting a therapeutic mechanism whereby mulberry fruit causes a change in the microbiota, leading to changes in microbial metabolites, which, in turn, improves colonic motility and secretion.

Sennoside A, the main active constituent of Da-Huang-Gan-Cao-Tang (Daiokanzoto, DKT), is converted by microbial β-glucosidases to generate rheinanthrone, the molecule with laxative activity. Because of the close connection between sennoside A and the gut microbiota, it was hypothesized that the therapeutic effect of sennoside A depends on the composition and function of the gut microbiota, which was proved in mice carrying different types of gut microbiota. Takayama *et al.* [103] proposed that different types of gut microbiota represent different 'patterns' defined by TCM and therefore they established a model to investigate the biological mechanisms behind the personalized medicinal practices in TCM. In DKT, sennoside A is mainly found in its herbal component of rhubarb. In fact, many other TCM formulations for the treatment of FC have a component of rhubarb, which was shown to increase intestinal secretion and improve stool consistency [104].

TCM usually takes the form of a complex composition and is multi-targeting. Understanding the links between changes in the composition of the intestinal flora, the altered gene expression of the intestines, and the metabolites produced after TCM therapy requires further investigation.

Conclusions

Microecological imbalance is an important feature in FC, which may contribute to the pathogenesis via multiple mechanisms mediated by microbial metabolites including BAs, SCFAs, 5-HT, and methane. The therapeutic effects of probiotics, prebiotics, synbiotics, and TCM often involve compositional and functional changes in the gut microbiota. Further studies on the pathomechanisms of FC and the therapeutic mechanisms of microecological agents will provide a knowledge base for better management of FC patients. Given the very different diet and the gut microbiota of laboratory animals compared to those of humans, understanding the therapeutic efficacy and the mechanisms of microecological agents may require adequately powered mechanistic clinical trials with FC patients.

Authors' Contributions

L.Q.Z. and L.X.Z. conceived of this work and designed the outlines of this review. S.S.Z. and L.X.Z. selected the references and prepared the first draft. All authors critically revised the manuscript and approved the final version for submission.

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Conflict of Interest

None declared.

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VacA 重组蛋白对 TRAF1/4-1BB/NF-κB 通路活化及胃上皮细胞增殖与凋亡的影响

袁玲芝　王芬

（中南大学湘雅三医院消化内科，湖南长沙 410013）

摘 要

背景和目的：项目组前期研究发现在 VacA+H.pylori 感染的胃粘膜组织中，TRAF1，4-1BB 及 IL-8 的表达显著升高，为进一步阐明 vacA 对 TRAF1/4-1BB/NF-κB 通路活化的影响，本研究构建 VacA 重组蛋白，通过体外实验模拟 VacA 毒素对胃上皮细胞的作用过程，初步验证“VacA→TRAF1→炎症 NF-κB 通路相关基因→IL-8”调控轴的存在，探索 H.pylori 毒力因子 VacA 蛋白致胃癌发生的作用机制。

方法：1.构建 VacA 重组蛋白，并进行体外生物活性检测；2.用不同浓度 VacA 重组蛋白刺激胃粘膜上皮细胞，分别通过 CCK8 细胞增殖试验及流式细胞学技术检测对细胞增殖与凋亡的影响；3.qRT-PCR、Western blot 检测对 TRAF1、4-1BB、Bcl-xl（抗凋亡蛋白）、Bax（促凋亡蛋白）表达的影响；4.qRT-PCR、ELISA 检测对 IL-8 表达的影响；5.通过 Western blot、细胞核浆分离技术、

细胞免疫荧光试验检测对 NF-κB 通路的活化。6.构建 BAY11-7082 介导的 NF-κB 通路抑制模型，同时用重组 VacA 蛋白刺激，上述相同方法检测对 TRAF1、4-1BB、IL-8、Bcl-xl、Bax 因子蛋白水平的变化及对靶细胞增殖、凋亡的影响。7.通过 siRNA 干扰技术沉默靶细胞 TRAF1 的表达，同时用重组 VacA 蛋白刺激，上述相同方法检测 TRAF1、4-1BB、Bcl-xl、Bax 因子的变化。

结果：1.成功构建具有生物活性的 VacA 重组蛋白；2.VacA 重组蛋白具有促进细胞凋亡、抑制细胞增殖的作用，且呈浓度依赖性（$P < 0.05$）；3.VacA 重组蛋白可使胃粘膜上皮细胞 4-1BB、IL-8、Bax 表达升高，Bcl-xl 表达下降，其中 TRAF1 在高浓度刺激组表达下降，在低浓度刺激组表达升高（$P < 0.05$）；4.VacA 重组蛋白可使磷酸化 p65、胞核蛋白 p65 表达显著升高，免疫荧光试验显示 p65 入核明显。5.阻断 NF-κB 通路，VacA 重组蛋白刺激靶细胞，TRAF1、4-1BB、IL-8、Bcl-xl、Bax 较单独刺激组表达下降（$P < 0.05$），且细胞凋亡率较前降低，细胞生长活力较前提升（$P < 0.05$）。6.沉默 TRAF1 的表达，低浓度 VacA 重组蛋白刺激靶细胞，4-1BB、Bcl-xl、Bax 较单独刺激组表达下降（$P < 0.05$）。

结论：VacA 重组蛋白刺激胃粘膜上皮细胞，上调 4-1BB 的表达，在 TRAF1 调控下激活 NF-κB 通路，促进炎症因子 IL-8 的表达，使促凋亡蛋白 Bax 表达升高，抗凋亡蛋白 Bcl-xl 表达降低，发挥促进细胞凋亡，抑制细胞增殖的作用，且呈浓度依赖性。

幽门螺杆菌耐药现状分析

吴聃 步光奎 廖江涛

湖南省人民医院（湖南师范大学附属第一医院）

目的：为了了解目前长沙地区幽门螺杆菌对 14 种不同抗生素的耐药情况。方法：收集 2020 年 4 月至 2021 年 5 月湖南省人民医院马王堆院区所有幽门螺杆菌培养阳性并完善体外药敏试验的 231 例患者资料，然后对耐药情况及性别、年龄、不同疾病进行统计学分析。

结果：幽门螺杆菌对阿莫西林、阿莫西林克拉维酸钾、头孢克肟、硫酸庆大霉素、四环素、盐酸多西环素、阿奇霉素、克拉霉素、左氧氟沙星、司帕沙星、甲硝唑、替硝唑、利福平、呋喃唑酮的耐药率分别为 6.49%、6.93%、7.79%、4.33%、6.06%、4.76%、16.02%、21.65%、7.79、6.49%、29.87%、19.48%、2.60%、3.03%；对于青霉素过敏者，四环素+甲硝唑、四环素+呋喃唑酮、四环素+左氧氟沙星、克拉霉素+呋喃唑酮、克拉霉素+甲硝唑、克拉霉素+左氧氟沙星的耐药率分别为 0.43%、0%、0%、1.73%、9.09%、0.87%；幽门螺杆菌对阿莫西林克拉维酸钾、司帕沙星、甲硝唑三种抗生素的耐药情况在不同性别组中的差异有统计学意义（P<0.05）；

幽门螺杆菌对甲硝唑的耐药情况在不同年龄组中的差异有统计学意义（P<0.05）；幽门螺杆菌对 14 种抗生素的耐药程度在不同疾病组中的差异无统计学意义（P>0.05）。结论：本研究中耐药率最高的是甲硝唑；阿莫西林克拉维酸钾及甲硝唑的幽门螺杆菌耐药率女性高于男性，而司帕沙星的幽门螺杆菌耐药率男性高于女性；随着年龄的增长，甲硝唑耐药率也在增加。

铋剂四联 10 天疗法联合酪酸梭菌、聚普瑞锌治疗幽门螺旋杆菌感染的疗效分析

王烁 1　彭芸　曾小明　高颖　高青　张桂英 2

（1. 湘雅常德医院消化内科 2. 湘雅常德医院消化内科）

目的：评价铋剂四联 10 天疗法联合酪酸梭菌、聚普瑞锌治疗幽门螺旋杆菌感染的疗效及安全性。方法：采用回顾性分析方法，收集 2018 年 07 月至 2021 年 7 月湘雅常德医院就诊使用铋剂四联 10 天疗法联合酪酸梭菌、聚普瑞锌治疗 Hp 感染的 209 例患者作为研究对象。

治疗方案：艾司奥美拉唑镁肠溶片（20mg）＋阿莫西林胶囊（1g）＋克拉霉素（0.5mg）＋胶体酒石酸铋胶囊（220mg）均 2 次/天，酪酸梭菌活菌片（350mg，3 次/天），疗程 10 天。后续追加艾司奥美拉唑肠溶片（20mg，1 次/天）＋酪酸梭菌活菌片（350mg，3 次/天）＋聚普瑞锌颗粒（75mg，2 次/天），疗程 14 天。结果：所有患者中，男性 85 例，女性 124 例，平均年龄 48 岁。按符合方案（PP）分析和按意向性（ITT）分析 Hp 根除成功率分别为 97.4%（189/194）和 90.4%（189/209），9 例（4.3%）患者在治疗期间出现不良反应，但程度均较轻微，可自行缓解。

结论：铋剂四联 10 天疗法联合酪酸梭菌、聚普瑞锌作为 Hp 感染的治疗方案，根除率高，安全可行，在缩短抗生素疗程同时不仅增加患者的依从性，也减少细菌耐药性的产生。

依从性良好幽门螺杆菌感染患者根除失败的危险因素

罗举；赵文芳；徐灿霞

中南大学湘雅三医院消化内科

背景：总所周知，依从性差是幽门螺杆菌根治失败的重要危险因素，但依从性良好的患者，铋剂四联 14 日疗法对幽门螺杆菌的根除率也在逐渐降低。

目的：通过一项回顾性、单中心研究，调查分析使用铋剂四联 14 日疗法且依从性良好的患者幽门螺杆菌根除失败的危险因素。

方法：纳入 2017 年 10 月至 2021 年 1 月就诊于湘雅三医院消化内科门诊，接受铋剂四联 14 日疗法根除幽门螺杆菌的患者，记录其基本信息、生活饮食习惯、诊疗经过及抗生素滥用史（患者没有获得医师处方或没有咨询医师自行购买抗生素服用）等，比较不同治疗方案亚组间的根除率，Logistic 回归分析根除失败的危险因素。

结果：最终纳入 972 例患者，男性 444 例（平均年龄 43.7±12.9 岁），女性 528 例（平均 44.6±12.5 岁）。铋剂四联 14 日疗法根除成功 883 例，总根除率为 90.8%。初治者根除率为 91.4%，复治者根除率为 83.5%。其中含阿莫西林和呋喃唑酮组 33 例（根治率为 93.9%），含阿莫西林和多西环素组 184 例（根治率为 92.3%），含多西环素和呋喃唑酮组 706 例（根治率为 90.7%），含阿莫西林和克拉霉素组 49 例（根治率为 83.6%）。

阿莫西林和克拉霉素组方案的根除率明显低于其他三组。与根除成功组相比，根治失败组的平均年龄较大（50.7±11.1 岁 Vs 43.5±12.6 岁，P < 0.001），抗生素滥用史比例较高（29.2% Vs 12.1%，P < 0.001）。Logistic 回归分析发现年龄≥45 岁（OR：1.954；95%CI：1.176-3.248）和有抗生素滥用史（OR：2.245；95%CI：1.337-3.767）是根除失败的独立危险因素。

结论：年龄≥45 岁和有抗生素滥用史是导致依从性良好的幽门螺杆菌感染患者使用铋剂四联 14 日疗法根除失败的独立危险因素。

无症状幽门螺杆菌感染典型“鸡皮样胃炎”1 例诊治体会

湘雅常德医院　　伍丽

鸡皮样胃炎是以独特内镜下表现命名的一种特殊类型慢性胃炎。现通过对我院一例无临床症状的鸡皮样胃炎诊治经过及转归的报道，回顾有关鸡皮样胃炎与幽门螺杆菌(H. pylori)感染、胃癌相关性的文献，明确治疗鸡皮样胃炎的有效措施是根治幽门螺杆菌治疗，而行幽门螺旋杆菌培养+药敏等检测是提高根除率的有效手段。

结论：鸡皮样胃炎是一种内镜下表现为胃窦颗粒状及结节状改变为主的特殊类型胃炎，其发病与幽门螺杆菌感染有密切关系，大部分患者有上腹部疼痛不适等症状，亦可有患者无任何临床症状。国内外多项研究表明鸡皮样胃炎与胃癌的发生相关，可能是年轻人的胃癌发生的危险因素，因此对于幽门螺杆菌感染的无症状青年患者，易应当提倡完善胃镜检查。根除幽门螺杆菌是治疗合并 H. pylori 感染的鸡皮样胃炎有效手段，因其有部分抗生素耐药情况，我们认为采取幽门螺旋杆菌培养+药敏、耐药基因检测、宿主 CYP2C19 基因检测等是提高 H. pylori 首次治疗及复治根除率的有效手段，从而更好地遏制鸡皮样胃炎的进一步发展。

影响中国幽门螺杆菌初始根除治疗的相关临床因素的回顾性研究

唐艳波 唐国都 潘丽莹 朱华 周善梅 韦照永

柳州市人民医院消化内科

背景：由于抗生素的耐药率升高，幽门螺杆菌(Helicobacter pylori,H. pylori)的根除率逐年下降。实际上，在我国 H. pylori 感染患者中，除 H. pylori 耐药外，许多其他因素也可能影响 H. pylori 根除。

目的：分析影响 H. pylori 初始根除治疗的相关临床因素。

方法：本研究对 2015 年 1 月至 12 月在广西科技大学第一附属医院就诊的 264 例 H. pylori 相关性慢性胃炎和消化性溃疡（Peptic ulcer disease, PUD）患者进行了回顾性研究。患者被分成 3 组：ECA, RCA 和 RCM (R: 20 mg 雷贝拉唑, E: 40 mg 埃索美拉唑, C: 0.5 g 克拉霉素, A: 1.0 g 阿莫西林 和 M: 0.4 g 甲硝唑). 所有患者疗程为 14 天，随访 1 年。治疗结束后 4 周后复查 14 碳尿素呼气试验(14C-urea breath test, 14C-UBT)。结果 ≥40 岁患者的 H. pylori 根除率高于<40 岁患者（85.7% vs 54.7%, P=0.002）。

多变量分析显示只有年龄≥40 岁与 H. pylori 高根除率显著相关（OR4.58, P = 0.003）。十二指肠溃疡患者 H. pylori 根除率明显高于胃溃疡患者（79% vs. 60%, P = 0.012)。

结论：年龄是 H. pylori 根除成功的预测因素，十二指肠溃疡患者的 H. pylori 根除率高于胃溃疡患者，H. pylori 根除治疗与性别无关。

Efficacy of bismuth-based quadruple therapy for eradication of Helicobacter pylori infection based on previous antibiotic exposure: A large-scale prospective, single-center clinical trial in China

Jing-Jing Zhou 1,2 | Xiao Shi 1,2 | Shao-Peng Zheng 1,2 | Dan Tang 1,2 | Ting Cai 1,2 | Yao Yao 1,2 | Fen Wang 1,2

Abstract

Objective: This study aims to evaluate the efficacy and safety of three bismuth-based quadruple regimens for eradication of Helicobacter pylori (H pylori) infection in a large number of H pylori-positive patients with or without previous eradication therapy.

Methods: Consecutive adult patients with H pylori infection, regardless of previous eradication therapy, were eligible for the present study. Three bismuth-based quad-ruple regimens were selected according to the past history of antibiotics use: (A) esomeprazole, amoxicillin, clarithromycin, and colloidal bismuth tartrate;

(B) esomeprazole, amoxicillin, furazolidone, and colloidal bismuth tartrate; and (C) esomeprazole, doxycycline, furazolidone, and colloidal bismuth tartrate. All patients received a 14-day course of treatment, and 13 C/ 14 C urea breath test was utilized at four weeks after the completion of treatment to determine the H pylori eradication. Then, the eradication rates were calculated in terms of intention-to-treat (ITT) and per-protocol(PP) analyses. Adverse events (AEs) were recorded during the treatment.

Results: Overall, 1,226 patients were recruited, and 331, 57, and 838 patients were allocated to receive regimens A, B, and C, respectively. The H pylori eradication rates were 84.0%, 82.5%, and 82.9% (ITT) and 94.6%, 92.2%, and 93.7% (PP), respectively,in regimens A, B, and C. However, there was no significant difference among these three regimens. The incidence of AEs was 4.6% for all patients during the study, that is, 3.3%, 10.5%, and 4.7% for regimens A, B, and C, respectively. All AEs were mild and recovered at the follow-up visit.

Conclusion: All three bismuth-based quadruple regimens based on the previous antibiotic use can achieve satisfactory eradication rates for H pylori infection and are safe.

不同菌型 HP 与胃部疾病的相关性研究

赵文芳 湘雅三医院消化内科

背景：我国幽门螺杆菌（Helicobacter pylori，H. pylori）感染率目前为 50%左右，不同患者临床转归不同，这除了与宿主易感性及环境因素相关，更与所感染菌株的差异有关。

目的：探讨不同菌型 H. pylori 与胃部疾病的相关性及其致病性差异。

方法：纳入 2019 年 12 月至 2021 年 7 月就诊于湘雅三医院消化内科，同期行 H. pylori 抗体分型检测及胃镜/病理检查的患者。将胃部疾病分为慢性非萎缩性胃炎、消化性溃疡、慢性萎缩性胃炎/上皮内瘤变、胃癌 4 组；将 H. pylori 菌株根据抗体分型结果分为阳性、阴性 2 组，阳性组患者分为 I 型和 II 型 2 组，I 型组患者再分为 CagA（+）VacA（+）、CagA（+）VacA（-）、CagA（-）VacA（+）3 个亚组进行比较。统计分析不同 H. pylori 菌株与胃部疾病的相关性。

结果：共纳入 5133 例患者，HP 总感染率为 60.6%，各组 HP 感染率从高到低依次为胃癌组（78.6%）、慢性萎缩性胃炎组（78.3%）、消化性溃疡组（76.8%）、慢性非萎缩性胃炎组（52.5%），各组 HP 感染率比较，差异有统计学意义（$P < 0.05$），其中消化性溃疡组、慢性萎缩性胃炎组、胃癌组 HP 感染率均大于慢性非萎缩性胃炎组，差异有统计学意义（$P < 0.05$）；

HP 阳性患者中各组 I 型感染率从高到低依次为胃癌组（78.2%）、慢性萎缩性胃炎组（72.2%）、消化性溃疡组（68.7%）、慢性非萎缩性胃炎组（46.7%），各组间比较，差异有统计学意义（$P < 0.05$），其中消化性溃疡组、慢性萎缩性胃炎组、胃癌组的 I 型感染率均大于慢性非萎缩性胃炎组，差异有统计学意义（$P < 0.05$）；各组不同亚型 I 型 H. pylori 感染率比较，差异有统计学意义（$P < 0.05$），其中消化性溃疡组 CagA、VacA 双阳性率显著高于慢性非萎缩性胃炎组，差异有统计学意义（$P < 0.05$）。

结论：胃部疾病与 H. pylori 感染息息相关，且更为严重的胃部疾病，如消化性溃疡、慢性萎缩性胃炎、胃癌与 H. pylori 感染相较于慢性非萎缩性胃炎关系更为密切，H. pylori 感染率更高；相较于 II 型，I 型 H. pylori 更容易导致消化性溃疡、慢性萎缩性胃炎、胃癌；I 型 H. pylori 中 CagA、VacA 双阳性菌株占比大，与慢性非萎缩性胃炎比，更容易导致消化性溃疡。

布拉氏酵母菌辅助治疗幽门螺杆菌感染的随机对照研究

屈鹏 中南大学湘雅三医院

背景与目的:
幽门螺杆菌耐药率不断增加，常导致根除失败而需补救治疗，探索新的补救治疗方案具有重要临床意义。本研究比较布拉氏酵母菌联合铋剂四联初次治疗幽门螺杆菌感染，以及单用布拉氏酵母菌补救治疗幽门螺杆菌的疗效。探讨布拉氏酵母菌在治疗幽门螺杆菌感染中的应用价值，试验主要结局为根治率，次要结局为不良事件的发生率。

方法:
对于 2021 年 1 月至 9 月在中南大学湘雅三医院消化科门诊的患者，纳入 18 岁或以上、尿素呼气试验和/或组织病理学检查结果为幽门螺杆菌阳性；征求患者知情同意之后，对于初次治疗的 200 例随机分为两组分别给予 14 天布拉氏酵母菌联合铋剂四联(艾普拉唑 多西环素 阿莫西林 胶体酒石酸铋剂 布拉氏酵母菌,n=100)治疗以及 14 天铋剂四联（艾普拉唑 多西环素 阿莫西林 胶体酒石酸铋剂，n=100）的治疗，

而对两次以及两次以上治疗的 60 例患者随机分为两组，予以 14 天单一布拉氏酵母菌(n=30)或者继续 14 天的铋剂四联（艾普拉唑 多西环素 呋喃唑酮 胶体酒石酸铋剂，n=30）治疗，观察患者的治愈情况以及副作用发生情况，根除成功基于治疗后停药至少 4 周之后 C14 呼气试验的结果，分析患者的临床资料，包括患者的一般资料，治疗效果，服药情况，副作用等，评价布拉氏酵母菌对幽门螺杆菌感染初治以及补救治疗中的疗效。

结果：

根据目前的收集的数据分析表明，在初次治疗中，14 天布拉氏酵母菌联合铋剂四联治疗(艾普拉唑 多西环素 阿莫西林 胶体酒石酸铋剂 布拉氏酵母菌,n=100)根除率意向性分析、方案分析分为分别为 75.9% 、97.5%，对照组铋剂四联（艾普拉唑 多西环素 阿莫西林 胶体酒石酸铋剂,n=100）分别为 73.4%、95.5%，2 组比较均差异暂无统计学意义（P>0.05）,包含布拉氏酵母菌的铋剂四联组（2%）不良反应发生率要低于普通的铋剂四联组（9%）；在补救治疗中，单一布拉氏酵母菌（n=30）补救治疗的根治率意向性、方案分析分别为 58.8%、68.9% ，对照组铋剂四联（艾普拉唑 多西环素 胶体酒石酸铋剂 呋喃唑酮，n=30）分别为 83.3%、92.6%，

如果选取Δ=0.5，两者非劣效性分析无统计学差异（P>0.05），然而其中用布拉氏酵母菌补救治疗无出现不良反应，而铋剂四联组有 3 例出现恶 心、皮疹、上腹不适等症状，单用布氏酵母菌的不良事件的发生率低于铋剂四联组。

结论：

布拉氏酵母菌联合四联能够提高幽门螺杆菌感染的治愈率，减少不良事件的发生率，而单用布拉氏酵母菌补救治疗幽门螺杆菌感染有一定的治疗效果，可以做为补救治疗的过渡治疗方式，能够减少不良事件的发生率，提高患者的依从性，有待成为补救治疗的可选方案之一。

益君康辅助用于一例多次 Hp 根除失败患者的思考

董昀凡 南京市第一医院消化科

H.pylori 对抗生素耐药问题的日益严重,应用常规抗生素疗法治疗失败的患者也日益增多。本次汇报一例历经 5 年反复多次根除失败的难治性 H.pylori 感染患者，经过仔细询问病史资料及 Hp 药敏及基因型检测，给予精心设计的个体化根除方案辅以益生菌治疗，使患者的 H.pylori 最终成功获得根除，降低其胃癌发生风险，同时分享与讨论一些在临床根除幽门螺杆菌过程中的感悟。

中南大学湘雅医院
XIANGYA HOSPITAL CENTRAL SOUTH UNIVERSITY

幽门螺杆菌感染规范诊治

张桂英
中南大学湘雅医院
湘 雅 常 德 医院

幽门螺杆菌（HP）感染规范诊治

1. Hp概述
2. Hp感染的诊断
3. Hp感染规范化治疗

Hp概述

■ Hp是1982年由澳大利亚学者沃伦Robin Warren和马歇尔(Barry Marshall首次发现。

2005年诺贝尔医学奖获得者

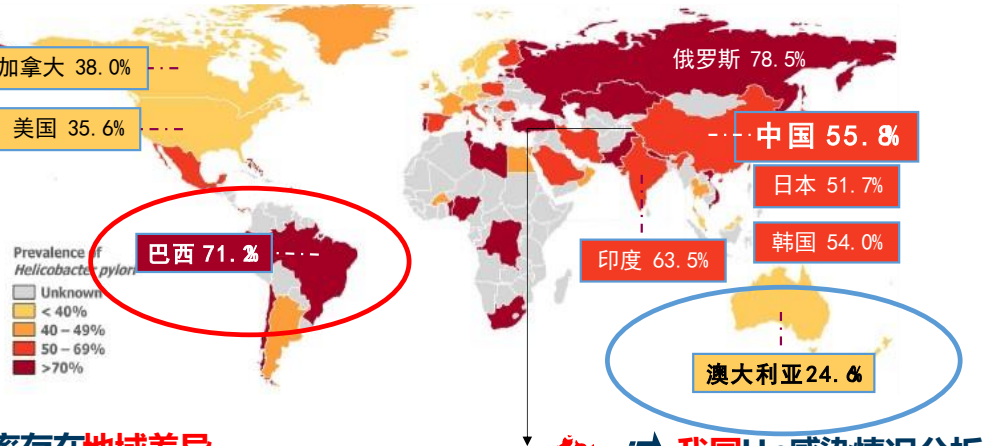
★表彰他们发现了导致胃炎和胃溃疡的细菌——幽门螺杆菌。

★通过发现Hp，使胃溃疡从原来的慢性病，变成了一种采用短疗程的抗生素和酸分泌抑制剂"就可治愈的疾病。

Hp感染了全球半数以上人口

★1970至2016年，来自62个国家的84项流行病学研究

★感染了全球至少43人[2]



➡ Hp患病率存在地域差异

非洲最高(70.1%，大洋洲最低(24.4%

➡ 与国家卫生地区经济发展情况有关

发展中国家远高于发达国家

尼日利亚最高(87.7%，瑞士最低(18.9%

➡ 我国Hp感染情况分析

22项 研究报告

10312例 参与者

估计感染率55.8%

1. Hooi JKY, et al. Gastroenterology 2017;153(2):420-429.
2. Shah S, et al. 2018 DDW Abstract Tu1662.

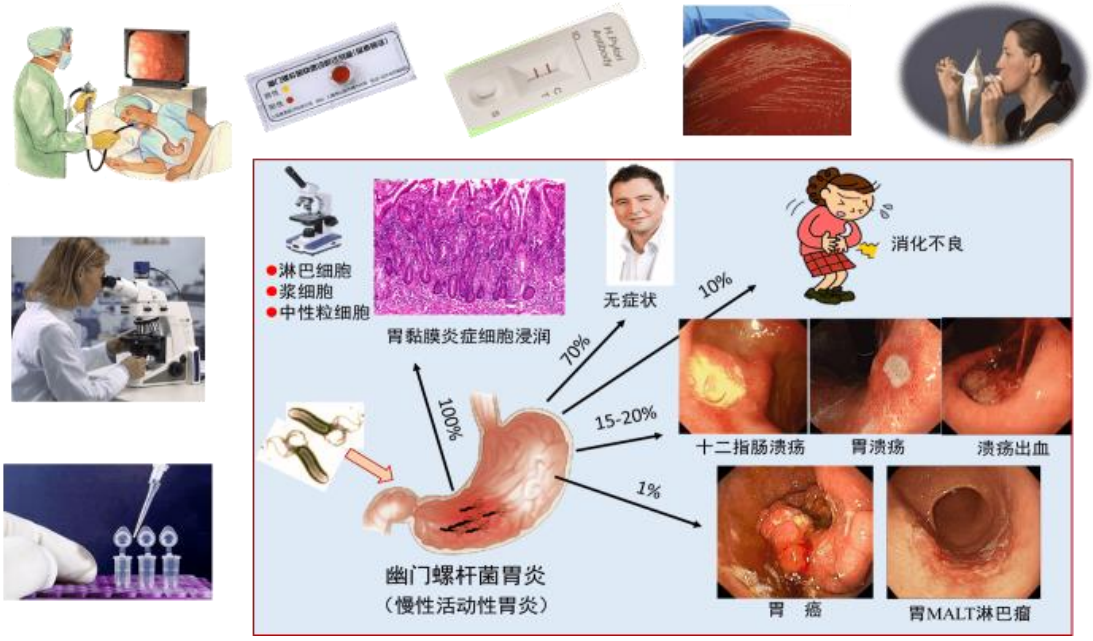
国际及地区Hp感染处理共识（近六年）

全球范围内Hp感染诊治受到持续关注。。。

幽门螺杆菌（HP）感染规范诊治

1. Hp概述
2. Hp感染的诊断
3. Hp感染规范化治疗

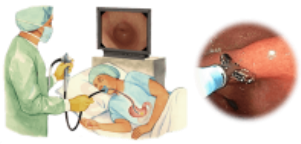
准确检测是有效处理的前提



Malfertheiner P. Nat Rev Gastroenterol Hepatol. 2014;11:628-38.
Sugano K,et al. Gut. 2015;64:1353-67 Graham DY. Gastroenterology. 2015;148:719-31.

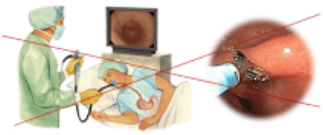
幽门螺杆菌检测方法

侵入性方法



- 内镜观察诊断
- 快速尿素酶试验
- 组织学检测
- 培养
- 分子生物学方法

非侵入性方法

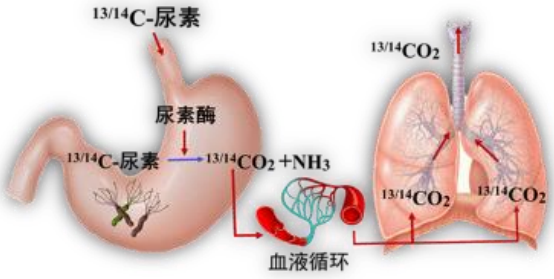


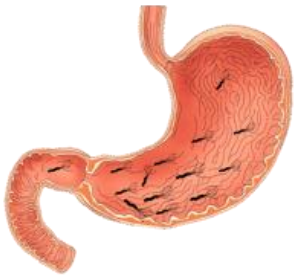
- 尿素呼气试验
- 粪便抗原试验
- 血清学试验
- 分子生物学方法

Wang YK, et al. World J Gastroenterol. 2015;21:11221-35 Atkinson NS, et al.Dig Dis Sci 2016:61:19–24

尿素呼气试验：优点

- 是最好的非侵入性方法，准确度高，易于操作。
- 可反映全胃幽门螺杆菌感染状况，克服细菌“灶性”分布差异、活检取材的影响。





Liu WZ, et al. J Dig Dis. 2013;14:211-21.

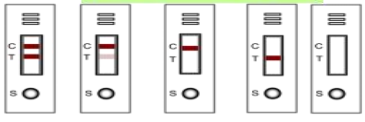
Atkinson NS, et al.Dig Dis Sci 2016:61:19–24　　Ferwana M,et al. World J Gastroenterol. 2015;21:1305-14

幽门螺杆菌粪便抗原试验

单克隆抗体检测粪便中幽门螺杆菌抗原

单份检测

结果判断



阳性　阴性　无效

多份检测

黄色为阳性

- 经过验证的单克隆抗体检测试剂具有较好的敏感性和特异性；
- 操作安全、简便、快速
- 不需要口服任何试剂，适用于所有年龄和类型患者。

Wang YK,et al. World J Gastroenterol. 2015;21:11221-35　　Atkinson NS, et al.Dig Dis Sci 2016:61:19–24

幽门螺杆菌血清学试验

- 不同试剂盒检测准确度差异较大；
- 幽门螺杆菌消失后抗体可长时间存在，一般不作为现症感染证据，不能用于治疗后复查。
- 主要用于流行病学调查

优点：检测结果不受近期用药和胃内局部病变影响

- 消化性溃疡出血
- 胃MALT淋巴瘤
- 胃严重肠化生/萎缩

其他方法检测阴性 → 血清学检测 → 阳 性 → 现症感染

Malfertheiner P, et al. Gut. 2012;61:646-64

Liu WZ, et al. J Dig Dis. 2013;14:211-21.

Atkinson NS, et al.Dig Dis Sci 2016:61:19–24

幽门螺杆菌感染的检测

感染诊断

1. 胃黏膜活检
   - 快速尿素酶试验
   - 组 织 学 检 测
2. 尿素呼气试验
3. 粪便抗原试验

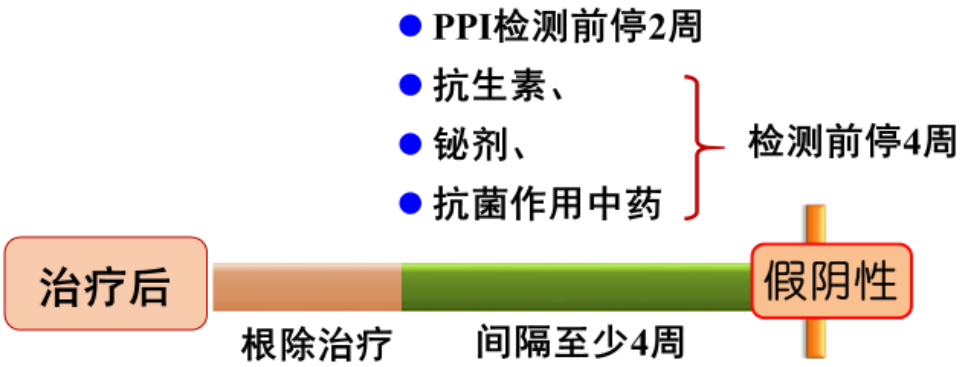
三项之一阳性 ↓ 感 染

判断根除

1. 尿素呼气试验
2. 粪便抗原试验

二项之一阴性 ↓ 根 除

是否根除的检测时机



Malfertheiner P, et al. Gut. 2012;61:646-64

Liu WZ, et al. J Dig Dis. 2013;14:211-21.

Atkinson NS, et al.Dig Dis Sci 2016:61:19–24

幽门螺杆菌（HP）感染规范诊治

1 Hp概述

2 Hp感染的诊断

3 Hp感染规范化治疗

根除幽门螺杆菌还需要指征吗？

幽门螺杆菌胃炎京都全球共识报告

幽门螺杆菌胃炎是一种感染（传染）性疾病 → 难以自愈 → 幽门螺杆菌感染者应给予根除治疗，除非有抗衡方面考虑。 → 似乎不再需要根除幽门螺杆菌指征。

- 推荐等级:强
- 证据级别: 高
- 共识水平:100%

- 推荐等级:强
- 证据级别: 高
- 共识水平:100%

Sugano K, et al. Gut. 2015;64:1353-67

根除幽门螺杆菌还需要指征吗？

幽门螺杆菌胃炎京都共识研讨会（2015.10, 上海）

幽门螺杆菌胃炎是一种感染（传染）性疾病 ↔ 存在矛盾心理 ↔ 幽门螺杆菌感染者应给予根除治疗，除非有抗衡方面考虑。

达成共识　　未达成共识

我国面临的现实：

- 人群中幽门螺杆菌感染率仍很高 (40%-60%)
- 幽门螺杆菌感染的人口基数颇大
- 幽门螺杆菌耐药率高，根除率下降或显著下降
- 有较高的再感染率
- 不正规应用抗生素包括根除幽门螺杆菌治疗问题突出

中华医学会消化病学分会幽门螺杆菌学组. 中华消化杂志 2016,36:53-57

美国共识和休斯顿共识

美国共识

All patients with a positive test of active infection with H. pylori should be offered treatment

HP感染检测结果阳性的患者都应接受治疗

休斯顿共识

Statement 1: We recommend that all patients with active *H. pylori* infection be treated.

陈述1：所有活动性幽门螺杆菌感染者都应接受治疗

El-Serag et al. *Clin Gastroenterol Hepatol* 2018 Mar 17.

我国2019版共识Hp根除指征

Hp阳性的下列疾病	强烈推荐	推荐
消化性溃疡(不论是否活动和有无并发症史	✓	
胃MALT淋巴瘤	✓	
慢性胃炎伴消化不良症状		✓
慢性胃炎伴胃黏膜萎缩、糜烂		✓
早期胃肿瘤已行内镜下切除或胃次全手术		✓
长期服用质子泵抑制剂		✓
胃癌家族史		✓
计划长期服用非甾体消炎药(NSAID)，包括低剂量阿司匹林		✓
不明原因的缺铁性贫血		✓
特发性血小板减少性紫癜		✓
其他Hp相关性疾病(如淋巴细胞性胃炎、增生性胃息肉、Ménétrier病)		✓
证实有Hp感染		✓

根除幽门螺杆菌获益存在差异

- 目前仍需要根除指征
- 根除指征推荐强度分级
- 多次治疗失败后需考虑获益风险比

刘文忠等. 中华内科杂志 2012:51:832-837. Malfertheiner P, et al. Gut. 2012;61:646-64

中华医学会消化病学分会幽门螺杆菌学组. 中华消化杂志 2016,36:53-57

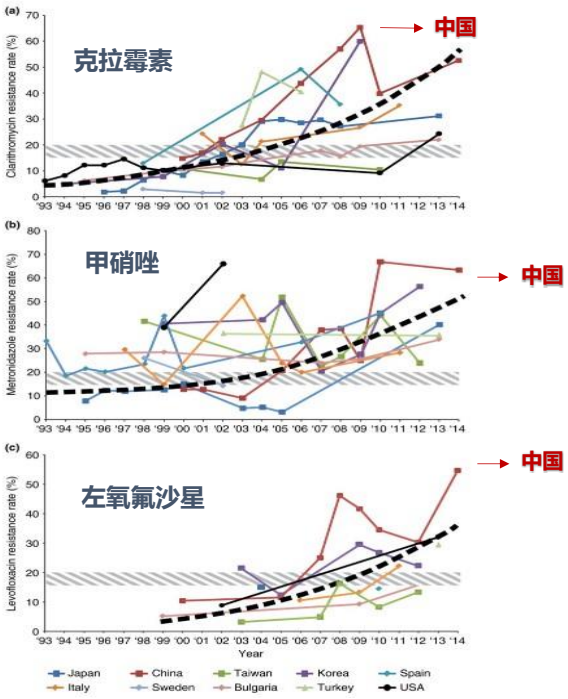
耐药情况

全球Hp抗生素耐药面临严重挑战

Review article: the global emergence of *Helicobacter pylori* antibiotic resistance

I. Thung, H. Aramin, V. Vavinskaya, S. Gupta, J. Y. Park, S. E. Crowe, M. A. Valasek

- 克拉霉素、甲硝唑、左氧氟沙星耐药率较高
- 特别是克拉霉素耐药率在快速上升
  - 日本和意大利约30%
  - 中国约50%
  - 土耳其约40%
  - 瑞典和台湾约15%
- 中国Hp抗生素耐药率排在全球首位
  （克拉霉素、甲硝唑和左氧氟沙星）



Thung I, et al. Aliment Pharmacol Ther 2016;43(4):514-33.

湘雅常德医院消化实验室550例患者Hp培养耐药情况

药物名称	总耐药率（N=550）	初治患者（n=309）	1次失败（n=108）	2次失败（n=87）	3次失败及以上（n=46）	全国数据
甲硝唑	86.2%	88.2%	83.6%	86.2%	90.6%	60-70%
克拉霉素	55.4%	40.3%	65.8%	75.6%	81.9%	20-45%
左氧氟沙星	43.5%	39.8%	42.6%	52.9%	62.3%	30-45%
阿莫西林	2.5%	1.8%	2.1%	2.6%	6.4%	0-5%
呋喃唑酮	1.4%	0.8%	1.5%	0.9%	3.8%	0-1%
四环素	3.5%	0%	5.7%	6.0%	6.7%	0-5%

Hp的耐药率随着根除次数的增加而递增。（数据来源上海芯超医学检验所2019.1-2021.7

湘雅常德医院消化实验室550例患者Hp培养耐药情况

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甲硝唑	86.2%	88.2%	83.6%	86.2%	90.6%	60-70%
克拉霉素	55.4%	40.3%	65.8%	75.6%	81.9%	20-45%
左氧氟沙星	43.5%	39.8%	42.6%	52.9%	62.3%	30-45%
阿莫西林	2.5%	1.8%	2.1%	2.6%	6.4%	0-5%
呋喃唑酮	1.4%	0.8%	1.5%	0.9%	3.8%	0-1%
四环素	3.5%	0%	5.7%	6.0%	6.7%	0-5%

Hp的耐药率随着根除次数的增加而递增。（数据来源上海芯超医学检验所2019.1-2021.7

抗Hp感染规范化治疗的两种基本策略：

经验性治疗

A

基于药敏试验的个体化治疗

B

不同国家地区的Hp耐药率，药物可获得性，经济条件都存在差异；Hp根除方案的选择应根据各地不同情况。

A：经验治疗方案的选择（遵循共识与指南进行治疗）

参考依据

1、当地抗生素的耐药率

2、可靠的临床试验结果

3、病人既往抗生素使用史

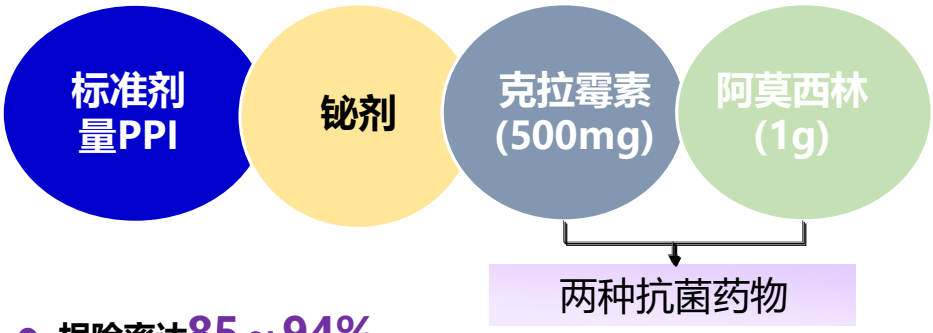
4、药物的可获得性

5、药物的潜在不良反应、患者经济条件

铋剂四联Hp的根除率

我国第五次全国共识推荐：

以PPI + 铋剂 + 2种抗菌药物的四联疗法



- **根除率达85～94%**

采用14d疗程，**根除率均>90%** 与伴同疗法相比，铋剂四联疗法减少了抗生素的使用剂量，且铋剂耐药率低，可额外提高耐药菌株根除率。多伦多共识、马五共识、ACG共识均推荐铋剂四联疗法为一线治疗方案。

中华医学会消化病学分会幽门螺杆菌和消化性溃疡学组. 中华消化杂志，2017,37(06): 364 -378.

标准三联加铋剂方案获国际同行好评

Bismuth improves PPI-based triple therapy for *H. pylori* eradication

Peter Malfertheiner

铋剂提高了PPI为基础三联疗法Hp根除率

该文作者是Maastricht -2,-3,-4 Hp 感染处理共识的第一作者

Maastricht-3

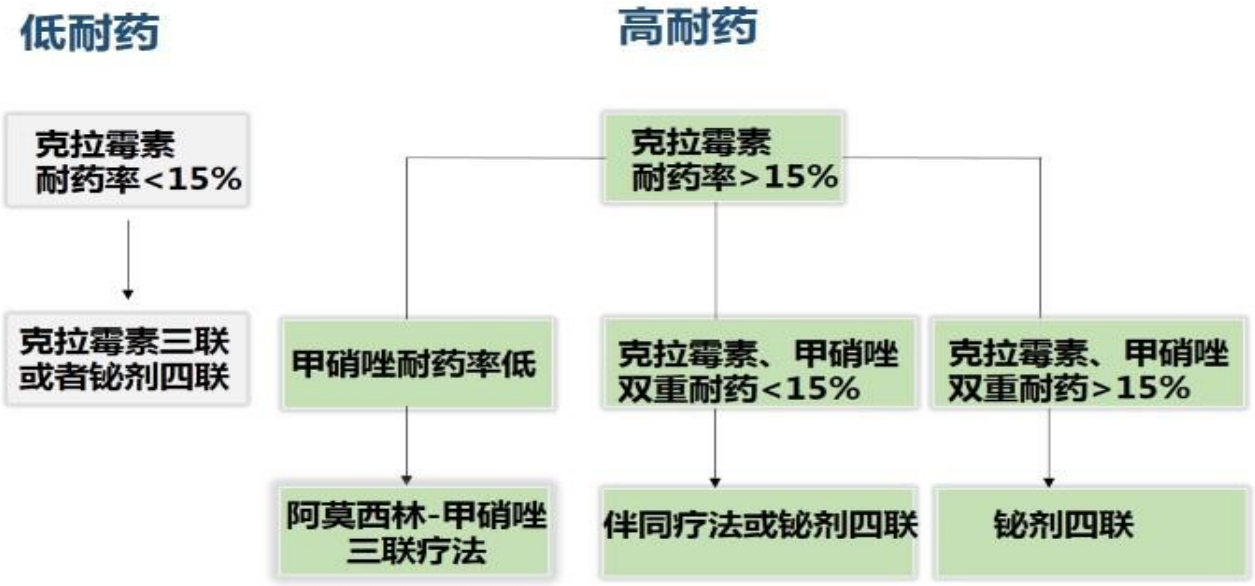
如当地Hp对克拉霉素耐药率 >15%-20%，就不应使用克拉霉素或应在使用前行药敏试验。

在克拉霉素高耐药率地区，标准三联疗法加铋剂，延长疗程，不行药敏试验，仍可应用。

Malfertheiner P. Nat Rev Gastroenterol Hepatol. 2010 ;7:538-9

马五共识推荐的一线治疗方案

根据克拉霉素耐药率的不同选择根除方案



Malfertheiner P, et al.*Gut* 2017;66:6–30.

共识推荐7种铋剂四联方案

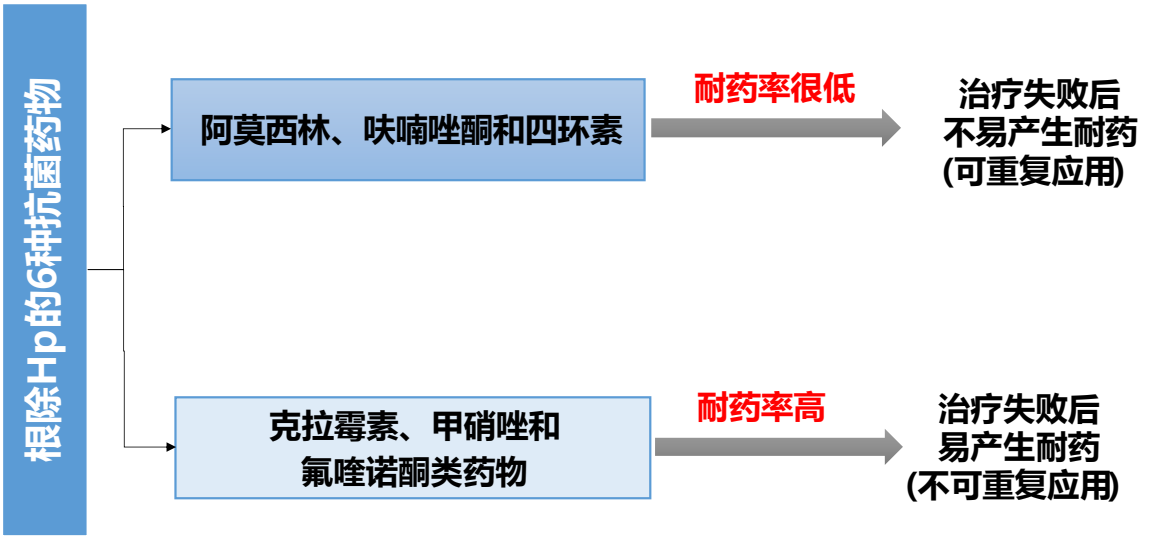
编号	1	2	3	4	5	6	7
抗生素组合	阿莫西林	阿莫西林	四环素	四环素	阿莫西林	阿莫西林	阿莫西林
	克拉霉素	呋喃唑酮	呋喃唑酮	甲硝唑	左氧氟沙星	四环素	甲硝唑

第四次全国幽门螺杆菌感染处理共识会议推荐（2012）

第五次共识会议推荐（2016）

◆ 提高首次治疗的根除率

- 提高Hp根除率：充分考虑药物的耐药特性及用药史



中华医学会消化病学分会幽门螺杆菌学组 . 胃肠病学 2012; 17(10):618 -625.

◆ 补救治疗方案选择原则

- 应参考以前用过的方案
- 不重复原方案
- 不重复用克拉霉素或左氧氟沙星
- 重复应用甲硝唑需优化剂量

一项前瞻性、单中心临床试验研究

Efficacy of bismuth-based quadruple therapy for eradication of *Helicobacter pylori* infection based on previous antibiotic exposure: A large-scale prospective, single-center clinical trial in China

Regimen	Successful eradication	Eradication rate	
		ITT (95% CI)	PP (95% CI)
A (n = 331)	278	84.0% (80.1%-87.9%)	94.6% (92.5%-97.5%)
B (n = 57)	47	82.5% (72.0%-92.0%)	92.2% (84.6%-99.5%)
C (n = 838)			
First-line regimen (n = 753)	624	82.9% (80.2%-85.6%)	94.5% (92.8%-96.2%)
Rescue regimen (n = 85)	71	83.5% (75.6%-91.4%)	86.6% (79.2%-94.0%)

结论：基于既往抗生素的使用史，采用不同抗生素组合的铋剂四联方案治疗，均显示满意的*Hp*根除率。

A：埃索美拉唑+阿莫西林+克拉霉素+胶体酒石酸铋;B：埃索美拉唑+阿莫西林+呋喃唑酮+胶体酒石酸铋；
C：埃索美拉唑+多西环素+呋喃唑酮+胶体酒石酸铋。

ZHOU J J, SHI X, ZHENG S P, et al.Helicobacter, 2020, 25(6): e12755

我院铋剂四联10天疗法联合酪酸梭菌、聚普瑞锌*Hp*根除率疗效

湘雅常德医院消化内科 2018年7月-2021年7月）

	PP分析	ITT分析
Hp根除率	97.4%（189/194）	90.4%（189/209）

强化杀菌（10天）：第一阶段 艾司奥美拉唑 + 阿莫西林 + 克拉霉素 + 铋剂 + 酪酸梭菌
巩固维持（14天）：第二阶段 艾司奥美拉唑 + 聚普瑞锌 + 酪酸梭菌

- 铋剂四联10天疗法联合酪酸梭菌、聚普瑞锌作为*Hp*感染的治疗方案，根除率高
- 安全可行，在缩短抗生素疗程同时不仅可增加患者的依从性，也可减少细菌耐药性的产生。

中国现代医学杂志待发表

益生菌的使用可提高p根除率，减少并发症

组别	失访例数	完成例数	根除成功例数	H.pylori根除率/%	
				ITT分析	PP分析
A组	18	132	81	54.0	61.4
B组	13	137	115	76.7①	83.9①
C组	14	136	106	70.7①	77.9①
D组	10	140	130	86.7①②	92.3①②
χ^2值	–	–	–	41.872	42.443
P值	–	–	–	0.000	0.000

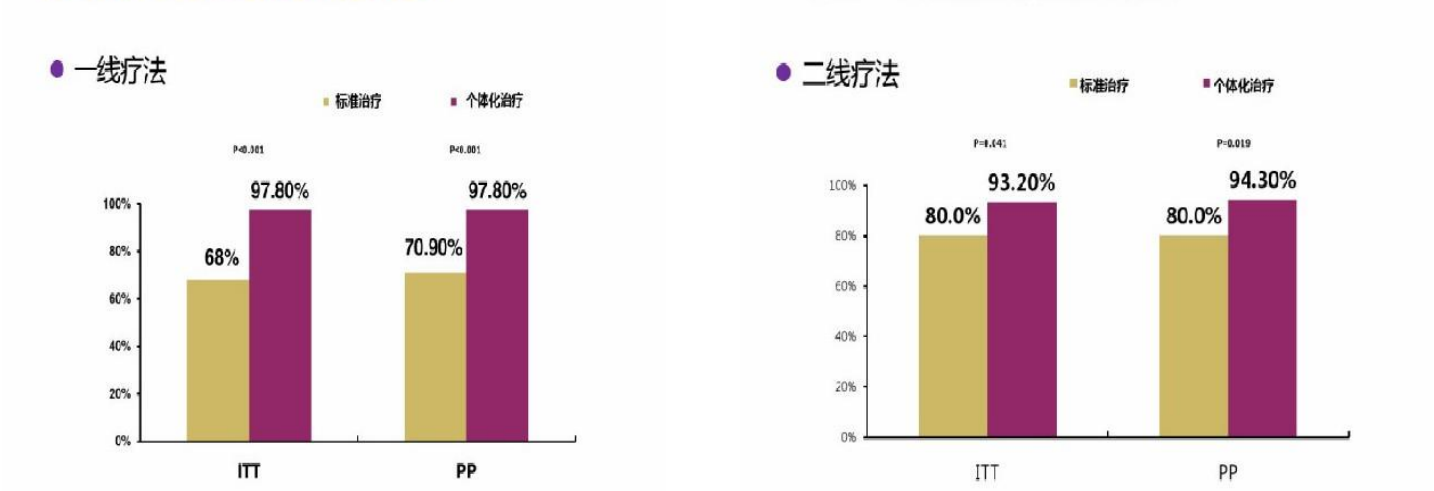
注：①与A组比

组别	阿莫西林胶囊	克拉霉素缓释片	雷贝拉唑钠肠溶片	胶体果胶铋胶囊	复方嗜酸乳杆菌片	疗程
A组	1.0 g/次，2次/d	500 mg/次，2次/d	20 mg/次，2次/d	200 mg/次，2次/d	–	10 d
B组	1.0 g/次，2次/d	500 mg/次，2次/d	20 mg/次，2次/d	200 mg/次，2次/d	–	14 d
C组	1.0 g/次，2次/d	500 mg/次，2次/d	20 mg/次，2次/d	200 mg/次，2次/d	1.0 g/次，3次/d	10 d
D组	1.0 g/次，2次/d	500 mg/次，2次/d	20 mg/次，2次/d	200 mg/次，2次/d	1.0 g/次，3次/d	14 d

2020年一项益生菌辅助含铋剂四联疗法根除幽门螺杆菌的临床研究共随机纳入感染患者600例，使用益生菌组Hp根除率ITT86.7% PP92.3%

[1]周羽翔，郑欣晔，叶梦思，卢光荣，薛战雄．益生菌辅助含铋剂四联疗法根除幽门螺杆菌的临床研究［J］．中国现代医学杂志，2021，31(01)：68-73.

B：基于药敏及基因多态性的个体化治疗



无论是一线治疗还是二线治疗，Hp个体化治疗的根除率均高于标准治.（2014DDW）

药敏指导下的个体化治疗与经验性治疗在初次根除Hp疗效比

治疗方案	例数	根除成功	根除失败	根除率
经验性治疗	1023	936	87	91.5%
个体化治疗	130	127	3	97.7%
X^2				6.155
P值				0.013

湘雅常德医院消化内科（2019年1月-2021年7月）

P值＜0.05，两组之间差异有统计学意义，
个体化治疗相对于经验性治疗成功率更高。

根据Hp药敏及基因检测个体化治疗

Hp感染复治及难治性Hp感染的疗效观察

治疗次数	根除率
复治根除率（根除失败1次）	96.4%（54/56）
复治根除率（根除失败2次）	91.4%（32/35）
难治性根除率（根除失败≥3次）	85.7%（24/28）

湘雅常德医院消化内科（2019年1月-2021年7月）

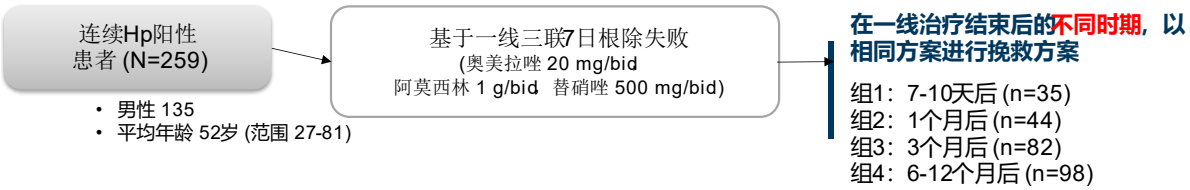
胡伏莲教授报道例难治性幽门螺杆菌感染治疗2次失败，经下述治疗后，根除成功

疗程	药物
第1~14天	荆花胃康胶丸2粒 tid 餐前:双歧三联活菌(培菲康)2 粒 tid 餐后
第15~28天	E+Tc+F+Bi;E40 mg tid餐前:胶体果胶铋150 mg tid;餐前 Tc 500 mg tid 餐后:F100 mg tid 餐后
第19~42天	荆花胃康胶丸 2粒 tid 餐前:双歧三联活菌(培菲康)2粒 tid 餐后:胶体果胶铋 100 mg tid 餐前

文献来源：娜日格乐,成虹,胡伏莲. 难治性幽门螺杆菌感染治疗成功1例报道[J]. 胃肠病学和肝病学杂志,2018,27(06):717-720.

Hp根除失败再次根除时间选择

首次根除治疗失败后再次根除治疗的时机2018年美国消化疾病周（DDW）上公布的一篇报告指出，根除治疗失败**半年后**再次根除治疗的根除率**约70%**，而一个月、三个月再治疗的根除率只有30%左右。



- 男性 135
- 平均年龄 52岁 (范围 27-81)

间隔时间	治愈患者数量	治愈率	P
7-10天	9/35	25.7	/
1个月后	14/44	31.8	/
3个月后	31/82	37.8	/
6-12个月后	69/88	70.4	0.01

Di Mario F, et al. 2018 DDW Abstract Tu1315.

Hp治疗新进展：大剂量阿莫西林

作者	年份及地区	组别	初治/复治	样本量（例）	治疗方案	根除率	不良反应发生率(%)
Yang等[2]	2019上海	大剂量组	初治	116	埃索美拉唑20 mg+阿莫西林750 mg日4次口服14 d	ITT:87.9% PP:91.1%	6.3
		含铋剂四联组	初治	116	埃索美拉唑20 mg+阿莫西林1000 mg+克拉霉素500 mg+铋剂1 g日2次口服14 d	ITT:89.7% PP:91.2%	22.8
Yu等[18]	2019上海	大剂量组	初治	80	埃索美拉唑40 mg日2次+阿莫西1000 mg日3次口服14 d	ITT:92.5% PP:96.1%	7.5
		含铋剂四联组	初治	80	埃索美拉唑40 mg+阿莫西林1000 mg+铋剂600 mg日2次口服14 d	ITT:88.8% PP:93.3%	11.3
Wei-Chen等[19]	2019中国台湾地区	大剂量组	初治	120	埃索美拉唑40 mg日3次+阿莫西林750 mg日4次口服14 d	ITT:91.7% PP:95.7%	9.7
		序贯四联组	初治	120	埃索美拉唑40 mg+克拉霉素500 mg+阿莫西林1 g+甲硝唑500 mg日2次口服14 d	ITT:86.7% PP:92%	27.5
田玲琳等[20]	2019山西	大剂量组	初治	55	埃索美拉唑20 mg日2次+阿莫西林1000 mg日3次口服14 d	80.8%	5.8
		四联组	初治	55	埃索美拉唑20 mg+阿莫西林1000 mg+呋喃唑酮100 mg日2次+荆花胃康2粒日3次口服14 d	81%	18.9
Yang等[21]	2015中国台湾地区	大剂量组	初治	150	雷贝拉唑20 mg+阿莫西林750 mg日4次口服14 d	95.3%	23.0
		四联组	初治	150	雷贝拉唑20 mg+阿莫西林1000 mg日2次口服10 d	85.3%	33.2
Yang等[21]	2015中国台湾地区	大剂量组	复治	59	雷贝拉唑20 mg+阿莫西林750 mg日4次口服14 d	89.3%	28.6
		四联组	复治	59	雷贝拉唑20 mg+阿莫西林1000 mg日2次口服10 d	51.8%	35.2
Seung等[22]	2011韩国	大剂量组	初治	104	兰索拉唑30 mg日3次+阿莫西林750 mg日3次		18.3
		三联组	初治	104	阿莫西林1000 mg+克拉霉素500 mg+兰索拉唑30 mg日2次	82.8%	35.6

研究证实，大剂量双联方案可获得与四联及三联方案同样的效果，且副反应较少，值得期待

[1]曲素萱,Moussa Harouna Koumba,王东旭,郭雪云,林连捷. 大剂量双联方案在根除幽门螺杆菌中的应用进展[J]. 中国实用内科杂志,2021,41(01):64-67+71.

新的Hp治疗进展：沃诺拉赞

	PPI group	Vonoprazan group	*P* value
Primary eradication therapy			
ITT analysis	73.2% (1259/1720)	85.7% (287/335)	< 0.0001
PP analysis	76.4% (1259/1647)	90.3% (287/318)	< 0.0001
Secondary eradication therapy			
ITT analysis	89.9% (347/386)	89.4% (59/66)	0.87
PP analysis	92.8% (347/374)	96.7% (59/61)	0.4

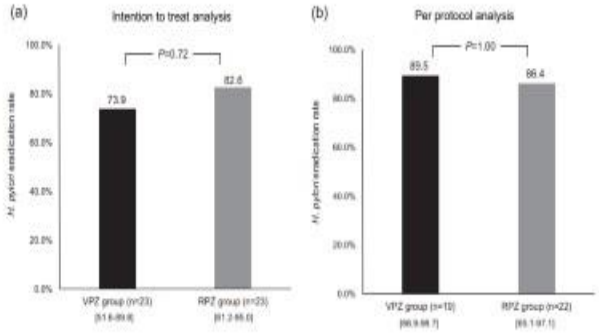


Figure 2. Comparison of *Helicobacter pylori* eradication rates in the VPZ and RPZ groups in (a) ITT analysis; and (b) PP analysis. Number of patients is shown in parentheses. 95% CIs are shown in square brackets. *P* values were calculated by Fisher's exact test.
CI, confidence interval; ITT, intention to treat; PP, per protocol; RPZ, rabeprazole; VPZ, vonoprazan.

沃诺拉赞组[VPZ40mg/天+阿莫西林1500mg/天+克拉霉素600mg/天]，7天
PPI组 阿莫西林1500mg/克拉霉素600mg/兰索/雷贝/艾司奥美拉唑,7天
以上方案为一线治疗，二线治疗克拉霉素换成甲硝唑500mg 治疗前先评估用药史

结论：沃诺拉赞对初次Hp治疗非常有效，可能成为一线抑酸药物

沃诺拉赞（VPZ）组[VPZ40mg/天+阿莫西林 AMPC 1500mg/天+甲硝唑（MNZ） 500mg/天]
雷贝拉唑（RPZ）组[RPZ20mg/天+AMPC1500mg/天+MNZ500mg/天）
结论： 作为二线治疗方案2组在疗效、和副反应上无显著差异

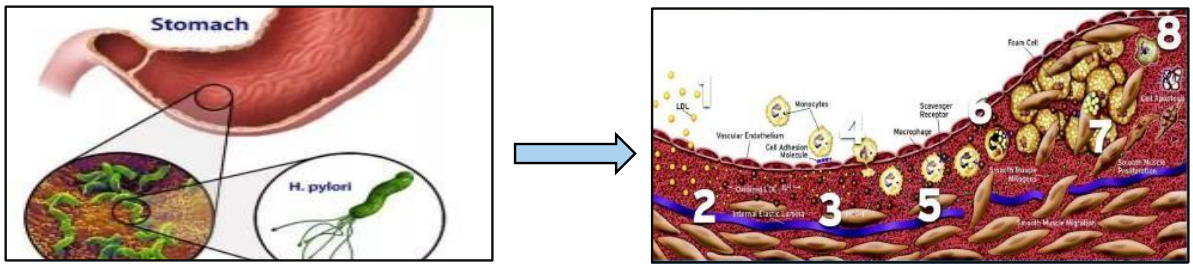
[1]Shinya Yamada, Takumi Kawakami, et al. Usefulness of vonoprazan, a potassium ion-competitive acid blocker, for primary eradication of Helicobacter pylori[J] World Gastrointest Pharmacol Ther 2016 November 6; 7(4): 555-55

[2]Mariko Hojo, Daisuke Asaoka et al. Randomized controlled study on the effects of triple therapy including vonoprazan or rabeprazole for the second-line treatment of Helicobacter pylori infection[J] Ther Adv Gastroenterol 2020, Vol. 13: 11

总结

- 经验治疗时放弃耐药性高的抗生素（以前的用药史）
- 依据当地抗生素耐药率的不同选择根除方案
- 推荐铋剂四联疗法为根除Hp的一线治疗方案，疗程10d或14d
- 初次治疗失败者，补救治疗的间隔时间推荐6个月
- 对于初治或多次治疗失败的患者宜行药敏及基因多态性检测，实行个体化治疗

幽门螺杆菌感染在动脉粥样硬化形成中的作用与机制



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随着人口老龄化，动脉粥样硬化等血管疾病发病率日益增加，缺血性肠病等导致消化道出血也随之增加，是全球范围内致死和致残的主要原因之一。

动脉粥样硬化等血管疾病危险因素包括：

可干预因素: 吸烟、高脂饮食、肥胖、高血压病、糖尿病等

不可干预因素: 如年龄、性别、遗传等

但仍有部分患者病因未明

进一步寻找和控制引起血管疾病的危险因素具有重要意义

新近研究认为，动脉粥样硬化等血管疾病是一种血管慢性炎症性疾病，这使得包括Hp在内的多种病原微生物感染是否通过引起炎症和免疫反应，促进血管疾病的发生发展成为近年来研究的前沿和热点。

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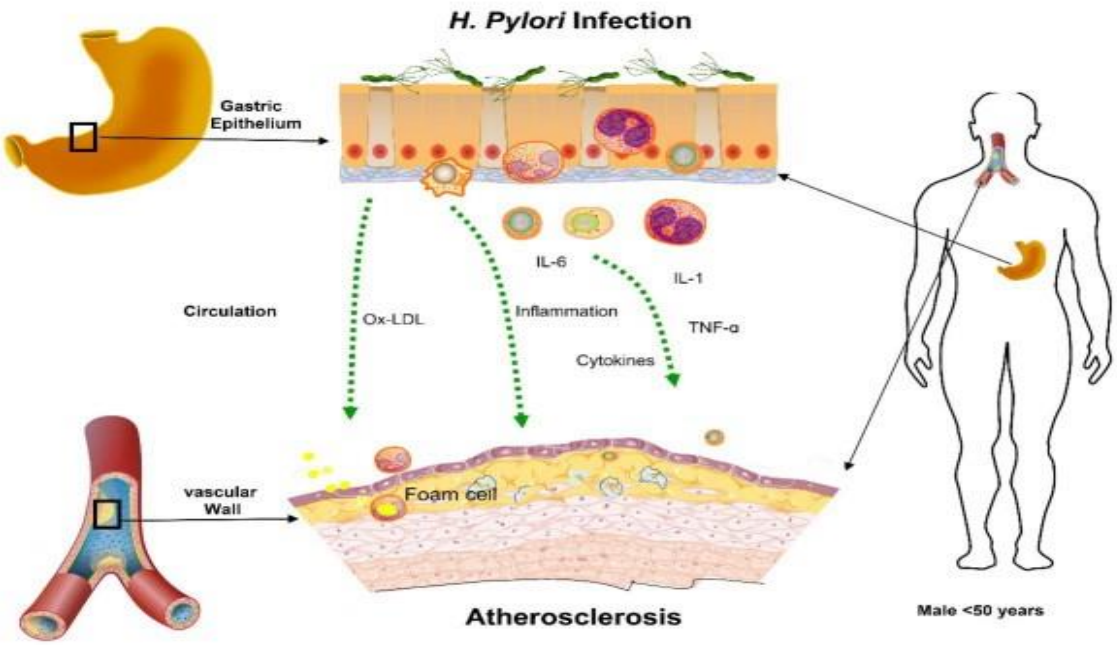

Hp与动脉粥样硬化疾病的相关性研究

Hp在动脉粥样硬化斑块形成中的作用

Hp致动脉粥样硬化的机制和途径

Hp与动脉粥样硬化疾病的相关性研究

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Hp与冠心病相关（第一篇： 1994 年)

- 研究对象： 111 例冠心病患者， 74 例正常对照组，白人男性 45 - 65 岁。
- 研究结果：冠心病组 66 例(59%) 有Hp，对照组 29 例(39%) 有Hp。在调整了一些冠心病的危险因素后， Hp与冠心病的关系仍有统计学意义。
- 作者当时推测 Hp与冠心病有关，可能系 Hp感染引起的慢性炎症反应所致。

Odds ratio for coronary heart disease among men who were seropositive for H pylori

*Effect of H pylori adjusted for:**	*Odds ratio (95% CI)*	*χ^2 (1 df)*	*p Value*
Unadjusted	2·28 (1·25 to 4·15)	7·35	0·007
Age, and risk factors†	2·26 (1·15 to 4·44)	5·71	0·02
Age, risk factors, and current social class	2·15 (1·07 to 4·29)	4·73	0·03
Age, risk factors, current social class and father's occupation	2·08 (1·03 to 4·20)	4·23	0·04
Age, risk factors, current social class and father's occupation, housing density, and hot water supply in the childhood home	1·90 (0·91 to 3·97)	2·97	0·09

* Adjusted by multiple logistic regression.
†Smoking history, age at starting smoking, lifetime cigarette consumption, history of high blood pressure, history of diabetes.

Mendall M A,Goggin P M,Molineaux N et al. Relation of Helicobacter pylori infection and coronary heart disease.[J] .Br Heart J, 1994, 71: 437-9.

Hp与动脉粥样硬化疾病的相关性研究

1997年柳叶刀指出：
94-97年，3年时间，至少20项研究（共约2600例患者）报道Hp与冠心病（19项）或中风（1项）有关。


THE LANCET
Volume 350, Issue 9075, 9 August 1997, Pages 430-436

Review

Chronic infections and coronary heart disease: is there a link?

Dr John Danesh MB [a] [b] [c], Prof Rory Collins MB [b], Prof Richard Peto FRS [b]

文章认为这种研究：

- 病理学的证据不足
- Hp与传统危险因素的相关性不强
- 在血管壁上还没有找到Hp

所以文章认为这种相关可能更多的是来自危险因素的残余混杂。

Danesh J,Collins R,Peto R,Chronic infections and coronary heart disease: is there a link?[J] .Lancet, 1997, 350: 430 -6.

Hp与动脉粥样硬化疾病的相关性研究

CagA与缺血性心肌病有关（1998年）

研究对象：

- 88例缺血性心肌病(age, 57±8 years; 74 men)
- 88例正常对照组(age, 57±8 years; 74 men)


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Association of Virulent *Helicobacter pylori* Strains With Ischemic Heart Disease

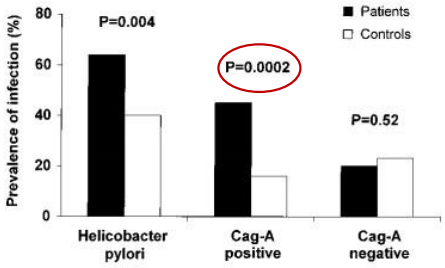


Figure 1. Prevalence of *Helicobacter pylori* infection and of cytotoxin-associated gene-A (CagA)–positive or CagA-negative strains in patients and controls.

缺血性心肌病CagA阳性率明显高于正常对照组

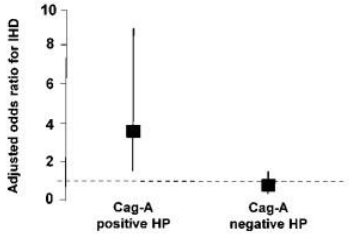


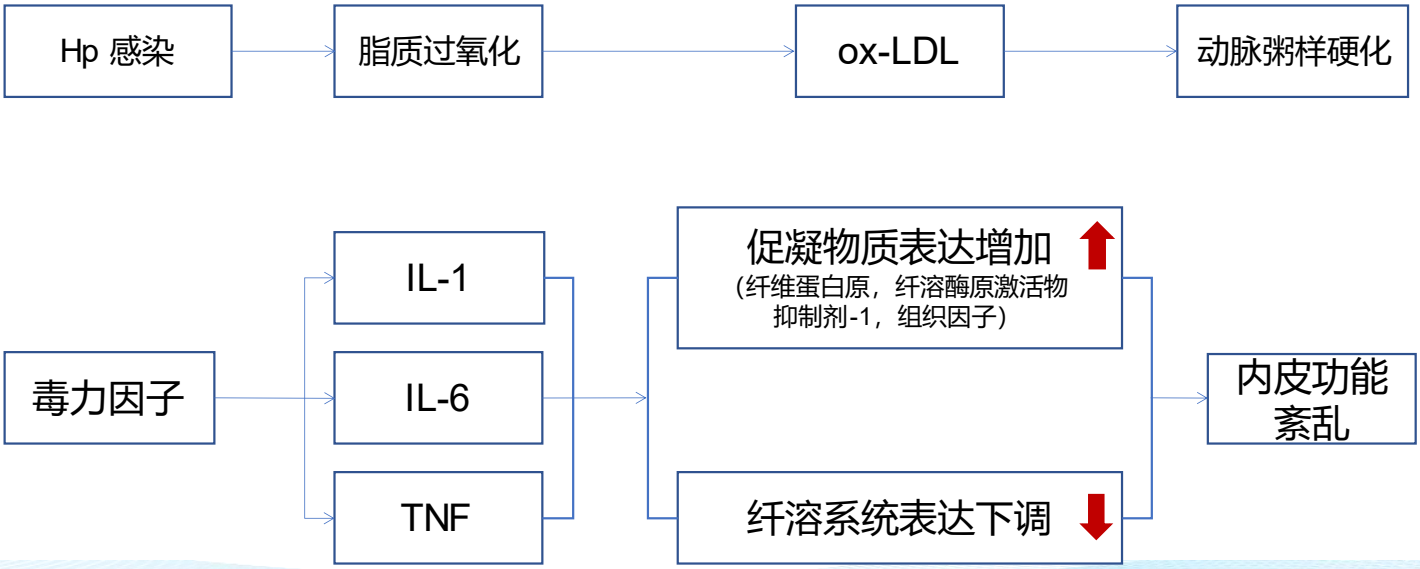
Figure 2. Adjusted odds ratios for ischemic heart disease associated with infection by cytotoxin-associated gene-A (CagA)–positive and CagA-negative *Helicobacter pylori*. IHD indicates ischemic heart disease; HP, *Helicobacter pylori*.

CagA阳性患缺血性心肌病的风险明显升高

Pasceri V,Cammarota G,Patti G et al. Association of virulent Helicobacter pylori strains with ischemic heart disease.[J] .Circulation, 1998, 97: 1675-9.

Hp与动脉粥样硬化疾病的相关性研究

当时作者推测的潜在机制



Pasceri V,Cammarota G,Patti G et al. Association of virulent Helicobacter pylori strains with ischemic heart disease.[J] .Cir culation, 1998, 97: 1675 -9.

Hp与动脉粥样硬化疾病的相关性研究

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Hp对冠心病预后的影响（2001年）

- 研究对象：1996年-1998年，连续入选1018名有症状，且有一支主要血管狭窄30%以上的患者。

TABLE 3. Seropositivity to Various Pathogens and Risk of Fatal Cardiovascular Event

Pathogen	Positive Serology, %		P		
	Deaths Due to Cardiovascular Causes (n=78)	Survivors (n=932)	Univariate	Adjusted*	HR (95% CI)*
CMV, IgG	80.8	70.7	0.06	0.3	1.4 (0.7–3.0)
HSV-1, IgG	94.9	92.7	0.5	0.3	3.0 (0.4–22.4)
HSV-2, IgG	25.6	13.5	0.003	0.045	2.0 (1.01–4.0)
EBV, IgG	100	98.7	0.3	0.98	. . .
EBV, IgA	27.8	13.8	0.001	0.001	2.8 (1.5–5.0)
C pneumoniae, IgG	84.6	84.7	0.99	0.9	0.9 (0.5–2.0)
C pneumoniae, IgA	46.2	48.6	0.7	0.4	0.8 (0.4–1.4)
H pylori, IgG	77.8	80.6	0.6	0.3	0.7 (0.4–1.4)
H pylori, IgA	41.0	27.7	0.01	0.002	2.5 (1.4–4.4)
M pneumoniae, IgG	57.7	59.9	0.8	0.6	0.8 (0.5–1.5)
M pneumoniae, IgA	16.7	12.3	0.3	0.3	1.5 (0.7–3.2)
H influenzae, IgG	82.1	74.1	0.1	0.5	1.3 (0.7–2.7)

Because of incomplete data of CRP and ejection fraction, total was 795 for the adjusted analyses.
*Adjusted for age, sex, presence or absence of ever smoking, diabetes, HDL cholesterol (continuous variable), number of stenoses, invasive treatment, antihypertensive treatment and statin intake at enrollment, CRP (logarithmically transformed continuous variables), and ejection fraction (<=30%).


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Impact of Viral and Bacterial Infectious Burden on Long-Term Prognosis in Patients With Coronary Artery Disease

- Hp感染是冠心病患者死亡的独立预测因子。
- 作者推测Hp感染有致动脉粥样硬化的作用，至少与其他已知的危险因子有协同作用。

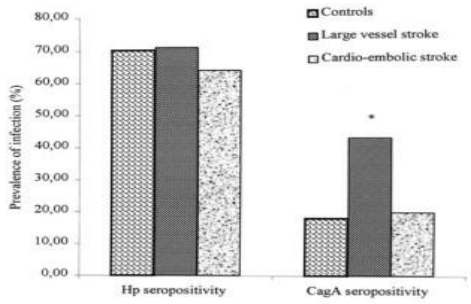
Rupprecht H J,Blankenberg S,Bickel C et al. Impact of viral and bacterial infectious burden on long -term prognosis in patients with coronary artery disease.[J] .Circulation, 2001, 104: 25-31.

Hp与动脉粥样硬化疾病的相关性研究

CagA与脑梗死（2002年）

研究对象：

- A组：138例脑血管源性脑梗死患者
- B组：61例心源性栓塞脑梗死患者
- 对照组：151例健康人群



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Prevalence of infection by CagA-positive *H pylori* in patients and control subjects. *P<0.01 in comparison to controls and to patients with cardioembolic stroke.


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Cytotoxin-Associated Gene-A–Positive *Helicobacter pylori* Strains Are Associated With Atherosclerotic Stroke

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- 三组的Hp阳性率没有差异。
- 脑源性大血管梗死组的CagA阳性率显著高于心源性梗死组，也显著高于正常对照组。
- 心源性梗死组和正常对照组之间没有差异。

Pietroiusti Antonio,Diomedi Marina,Silvestrini Mauro et al. Cytotoxin -associated gene -A--positive Helicobacter pylori strains ar e associated with atherosclerotic stroke.[J] .Circulation, 2002, 106: 580 -4.

Hp与动脉粥样硬化疾病的相关性研究

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Hp与冠脉钙化积分（2011年）

- 冠脉钙化积分是通过CT检测来衡量冠脉内斑块负荷的一项无创检测。

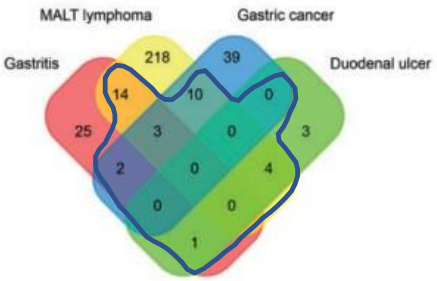
钙化积分	斑块负荷
0分	无明显斑块负荷
1-99分	轻度斑块负荷
100-399分	中度斑块负荷
≥400分	严重斑块负荷

- 不同的研究通过比较Hp感染状态与冠脉钙化积分的关系，提示Hp感染是CAD的独立的危险因素，且与早期冠脉硬化（0 < 冠脉积分 < 100）相关。

Park Min Jung,Choi Seung Ho,Kim Donghee et al. Association between Helicobacter pylori Seropositivity and the Coronary Artery Calcium Score in a Screening Population.[J] .Gut Liver, 2011, 5: 321 -7.
Lee M,Baek H,Park JS et al. Current Helicobacter pylori infection is significantly associated with subclinical coronary ather osclerosis in healthy subjects: A cross -sectional study.[J] .PLoS ONE, 2018, 13: e0193646.

Hp与动脉粥样硬化疾病的相关性研究

Hp的生物信息学研究

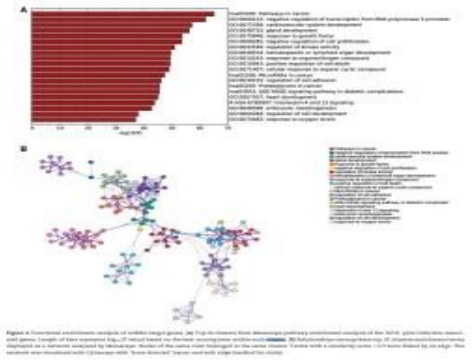


从4个疾病库中筛选表达差异的miRNA：
gastritis：45； duodenal ulcer：8；
gastric cancer：54；MALT lymphoma：249。

同时在2种疾病中表达差异的有34个miRNA，在这34个miRNA中：**hsa-let-7c, hsa-miR-204** 和 **hsa-miR-551b**同时出现在3个疾病库中。

34个miRNA涉及调控765个靶基因：

红色的三角形是miRNA
绿色的椭圆形是受调控的基因



再从765个靶基因中找到20个最相关的基因簇：

前3位涉及的功能是：

- 肿瘤，
- RNA聚合酶II启动子转录的负调控，
- 心血管系统的发育。

Yang Jue,Song Hui,Cao Kun et al. Comprehensive analysis of Helicobacter pylori infection -associated diseases based on miRNA -mRNA interaction network.[J] .Brief. Bioinformatics, 2019, 20: 1492 -1501.

Hp与动脉粥样硬化疾病的相关性研究

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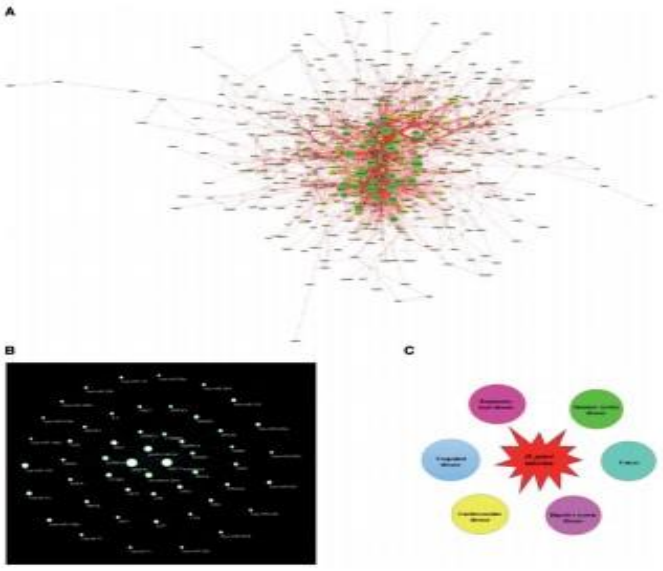
Hp的生物信息学研究



通过蛋白互作选出20个中枢基因

最后得出Hp感染相关的六种疾病

1. 消化系统疾病
2. 心血管系统疾病
3. 肿瘤
4. 免疫系统疾病
5. 呼吸系统疾病
6. 泌尿系统疾病

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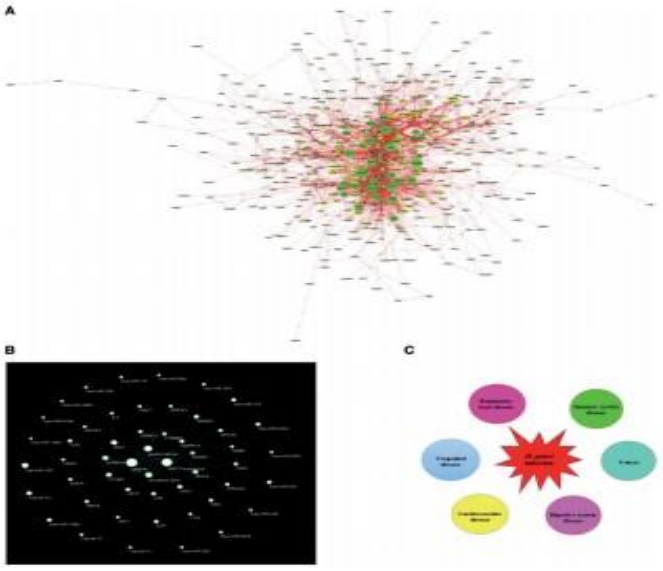

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幽门螺杆菌与动脉粥样硬化疾病的相关性研究

近5年来幽门螺杆菌感染与其他动脉粥样硬化相关的临床研究

疾病	年份	方法	人群	病例数（人）	结果和意义
高血压病	2018	横断面研究	中国	5246	Hp感染与舒张压及平均动脉压的升高相关。
	2019	前瞻性队列研究	中国台湾	106	与血清阴性孕妇相比，孕妇血清 Hp阳性与患妊娠期高血压的危险性高 (12%比1.2%，p=0.04)。
脑血管疾病	2020	Meta分析	韩国	5,541	根除Hp后能够降低脑血管疾病的死亡率 。
颈动脉粥样硬化	2016	病例对照	中国	354	Hp阳性患者颈动脉内中膜厚度和血清YKL-4水平明显高于Hp阴性患者。Hp诱导的炎症可能是血管性痴呆患者动脉粥样硬化的危险因素。
	2019	横断面研究	中国（湘雅三医院）	17613	**在小于50岁的男性中，Hp感染是颈动脉硬化独立的危险因素。持续感染 Hp的年轻男性新发颈动脉硬化的风险显著高于没有Hp 感染的人群*。**
糖尿病	2015	回顾性队列研究	中国台湾	811	Hp感染增加50岁以下居民的胰岛素抵抗和代谢综合征的风险。
	2019	横断面研究	阿富汗	271	Hp感染与糖尿病相关。

Zhang Linfang,Chen Zhiheng,Xia Xiujuan et al. Helicobacter pylori infection selectively increases the risk for carotid athero sclerosis in young males.[J] .Atherosclerosis, 2019, 291: 71 -77.

Hp与动脉粥样硬化疾病的相关性研究

在小于50岁的男性中，Hp感染是颈动脉硬化独立的危险因素。持续感染Hp的年轻男性新发颈动脉硬化的风险显著高于没有Hp感染的人群。

接受Hp治疗的年龄<65岁的年轻患者的累积冠心病发生率显著降低。

Hp感染与舒张压的升高相关

Hp感染是CAD的独立的危险因素，且与早期冠脉硬化（0 < 冠脉积分 < 100）相关

动脉粥样硬化是多种危险因素累积的结果，Hp极有可能在其他危险因素还没有参与或作用很弱的时候就已经参与了动脉粥样硬化的过程。

Hp在动脉粥样硬化斑块形成中的作用

- 动脉粥样硬化斑块是冠心病的病理学基础，一直是冠心病发病机制的研究重点。
- 许多研究关注Hp感染与动脉粥样硬化斑块的关系。

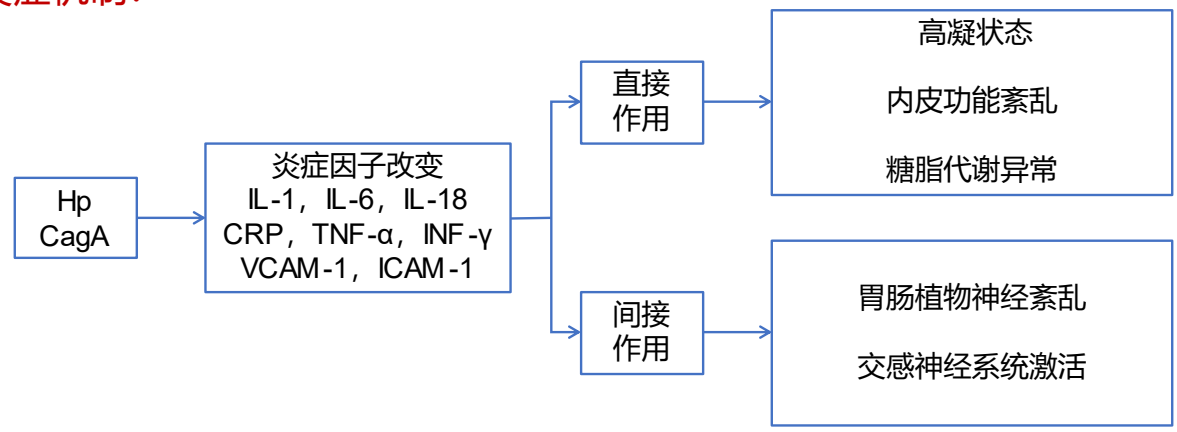
时间	期刊	支持	反对
2001	Stroke	1. 38例颈动脉粥样硬化的斑块标本中通过PCR的方法发现其中20例有Hp特异性的DNA片段； 2. 而这20例标本中有10例通过免疫组化进一步证实在斑块内有Hp抗体存在； 3. 而7例无颈动脉粥样硬化的尸检标本均未有阳性的发现。	
2002	Circulation	1. Hp的毒力因子CagA抗体能与血管壁上的抗原发生反应。	
2003	Digestive diseases and sciences		1. 32例患者的Hp-IgG抗体和肺炎衣原体-IgG抗体阳性率分别为72%和81%； 2. 血管壁和斑块的Hp培养和PCR检测均为阴性。但有3例在动脉粥样硬化斑块中扩增出肺炎衣原体DNA。

Hp在动脉粥样硬化斑块形成中的作用

时间	杂志	支持	反对
2006	Journal of clinical pathology		1. 在36例症状性颈动脉狭窄患者的组织标本中没有找到Hp特异性的DNA片段。
2012	Cardiovascular Pathology	1. 有研究从105例CABG病人取动脉粥样硬化斑块标本（其中53例同时取左乳内动脉标本）； 2. 其中31/105例（29.5%）用PCR的方法检测到Hp特异性的16S rRNA； 3. 而53例左乳内动脉标本均未检测到。	
2019	PLOS ONE	1. Hp感染的猴子，特别是CagA阳性的猴子动脉粥样硬化斑块大小和内中膜增厚的程度都明显大于未感染Hp的猴子; 2. 胃内单位体积下的Hp特异性的16S rRNA的表达水平与动脉相同体积下Hp特异性的16S rRNA的表达水平成线性正相关。	

Hp感染致动脉粥样硬化的机制

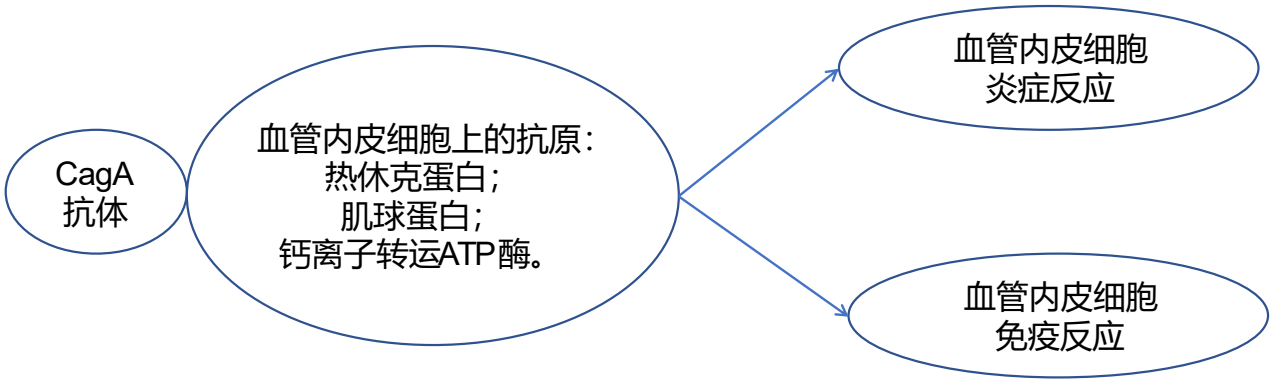
1、炎症机制：



Pothineni Naga Venkata K,Subramany Swathi,Kuriakose Kevin et al. Infections, atherosclerosis, and coronary heart disease.[J] .Eur. Heart J., 2017, 38: 3195 -3201.

Hp感染致动脉粥样硬化的机制

2、免疫机制：抗原与抗体结合引起局部的免疫反应和炎症反应



Budzyński, J., et al., Association between Bacterial Infection and Peripheral Vascular Disease: A Review. International Journ al of Angiology, 2016. 25(01): p. 003-013.

Hp感染致动脉粥样硬化的机制

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3、脂质代谢异常：

- Hp感染的人群往往表现出更高的甘油三脂以及VLDL水平，更低的HDL水平。
- 还有一些观点认为Hp能够促进LDL转化为ox-LDL。
- 根除Hp能使HDL上升也进一步证明了Hp感染可以影响脂质代谢。

Kim, T.J., et al., Helicobacter pylori is associated with dyslipidemia but not with other risk factors of cardiovascular dise ase. Scientific reports, 2016. 6(1): p. 38015.

Hp感染致动脉粥样硬化的机制

4、血小板激活：

（1）Hp能够与血管性血友病因子（vWf）结合并通过血小板膜糖蛋白Ib（GPIb）激活血小板。

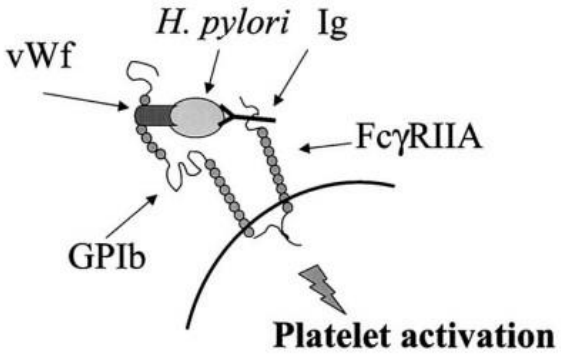
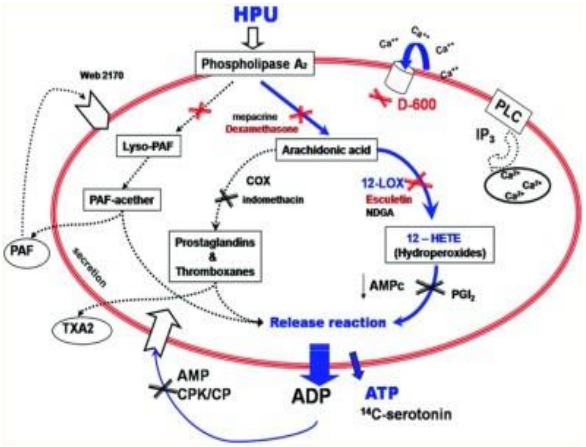


Figure 6. Interaction between *H. pylori* and a platelet that leads to platelet activation.

（2）Hp尿素酶与磷脂酶A2结合，通过花生四烯酸和脂氧合酶途径促进ADP的释放，诱导血小板的活化和聚集。



HPU+ 磷脂酶 A2

↓

花生四烯酸

↓ 12-脂氧合酶

12羟二十烷四烯酸

（过氧化氢）

↓

ADP/ATP

Byrne, M.F., et al., Helicobacter pylori binds von Willebrand factor and interacts with GPIb to induce platelet aggregation. Gastroenterology, 2003. 124(7): p. 1846 -1854.
Wassermann, G.E., et al., Helicobacter pylori urease activates blood platelets through a lipoxygenase -mediated pathway. Journal of Cellular and Molecular Medicine, 2010. 14(7): p. 2025 -2034

Hp感染致动脉粥样硬化的机制

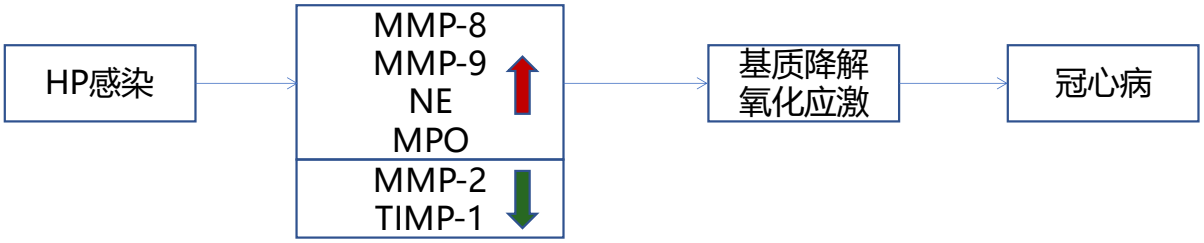
5、氧化应激：

- 氧化应激在动脉粥样硬化斑块形成中占有重要的作用，其存在于动脉粥样硬化从脂纹病变到斑块破裂的整个发生、发展过程中。
- 氧化应激的水平可以用活性氧（ROS）的水平来反应。

ROS增加 → 血管功能障碍 → 动脉粥样硬化

Hp感染致动脉粥样硬化的机制

- 有研究发现Hp感染组的患者外周血活性氧（ROS）水平明显增加，而根除Hp后ROS明显下降；
- 有研究比较Hp阳性的胃炎组与健康对照组的金属基质蛋白酶的水平发现Hp阳性组的MMP-8，MMP-9，NE，MPO水平较对照组明显升高，MMP-2，TIMP-1水平下降。研究结果显示Hp感染患者可能具有更强的胶原蛋白降解和氧化应激水平，从而导致冠心病。



Mashimo M,Nishikawa M,Higuchi et al. Production of reactive oxygen species in peripheral blood is increased in individuals with Helicobacter pylori infection and decreased after its eradication.[J] .Helicobacter, 2006, 11: 266-71.
HI, R., et al., Enhanced systemic matrix metalloproteinase response in Helicobacter pylori gastritis. Annals of medicine, 2009. 41(3): p. 208-15

Hp感染致动脉粥样硬化的机制

- 对氧磷酶1（PON1）是一种HDL相关性酯酶，有维持HDL基本结构及抗氧化抗炎的重要功能，它能保护LDL，使其不受氧化修饰，降低体内氧化型LDL的水平，是一种动脉粥样硬化的保护因子。
- Hp感染组PON1的水平较无感染组明显减低，提示Hp感染的抗氧化应激的能力和动脉粥样硬化保护作用明显下降。

Akbas, H.S., et al., The assessment of carotid intima media thickness and serum paraoxonase -1 activity in Helicobacter pylori po sitive subjects. Lipids in health and disease, 2010. 9(1): p. 92 -92.

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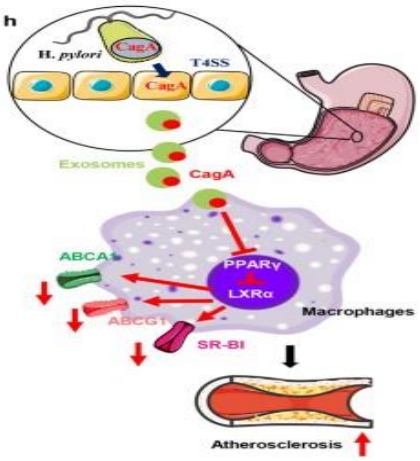
Hp感染致动脉粥样硬化的途径

- 在斑块和血管壁上找到Hp的痕迹，那么定植在胃内的Hp，其毒力因子是如何到达血管上的呢？
- 很有可能是通过外泌体！



- 含有CagA外泌体，被循环中的巨噬细胞吞噬
- 并促进巨噬细胞转变为泡沫细胞（胆固醇无法流出）
- 最终CagA随泡沫细胞沉积在血管壁上

Yang S,Xia YP,Luo XY et al. Exosomal CagA derived from Helicobacter pylori-infected gastric epithelial cells induces macrophagefoam cell formation and promotes atherosclerosis.[J] .J. Mol. Cell. Cardiol., 2019, 135: 46-51.

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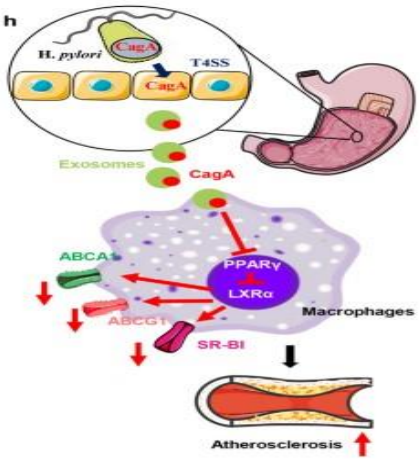

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我们的研究

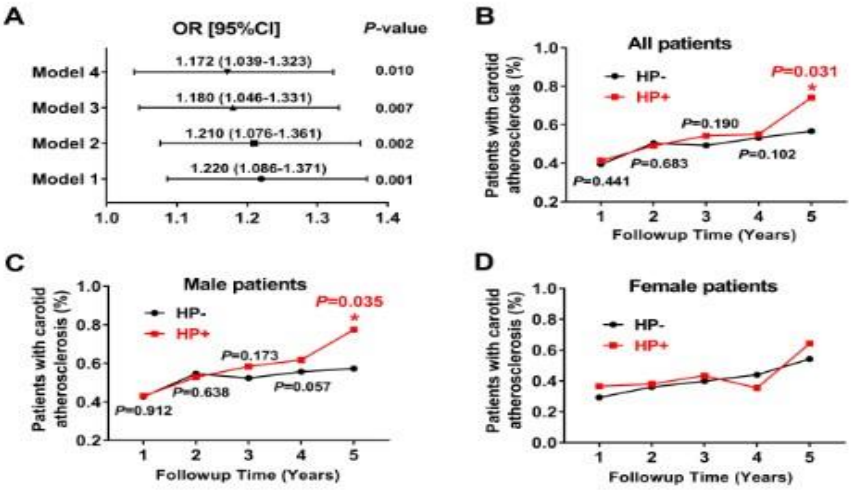


图1 人Hp感染与颈动脉硬化的相关性

Zhang, L.F., Chen Z.H., Xia, X.J., Chi, J.S., L.H., Liu, X.M., Li, R.,Li, Y.X.,Liu, D.,Tian, D.L.,Wang, H., Petroski, G.F. ,Flaker,G.C ., Hao, H., Liu, Z.G *.,Xu, C.X *. Helicobacter pylori infection selectively increases the risk for carotid atherosclerosis in young males. Atherosclerosis, 2019 DEC, 291：71-77.
（SCI收录，IF 3.919，JCR一区）

我们的研究

幽门螺杆菌感染致动脉粥样硬化的途径

1）健康体检人群中，Hp感染者较无Hp感染者血管内皮舒张功能减弱，抗Hp治疗后其血管内皮舒张功能有所恢复（图2）

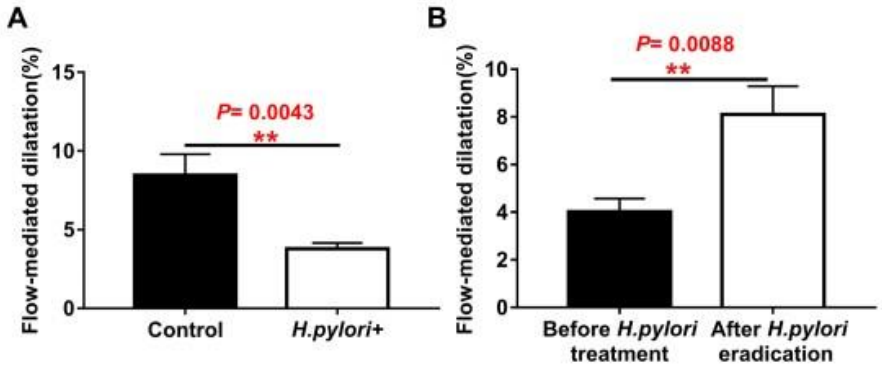


图2 Hp感染对体检人群血管内皮依赖性舒张功能的影响

我们的研究

2）C57BL/6小鼠体内实验 证实CagA⁺Hp感染可损伤血管内皮依赖性舒张功能抗Hp治疗可使血管内皮舒张功能部分恢复图4、图5）。

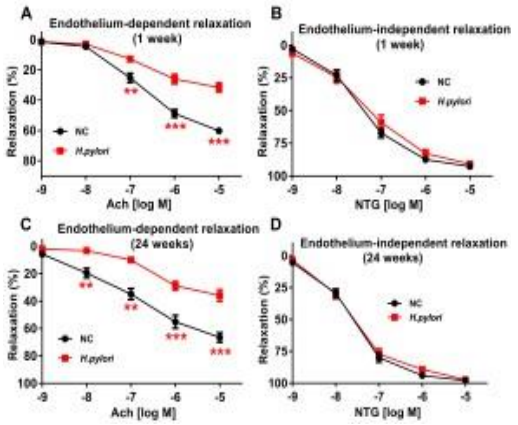


图3 Hp感染对C57BL/6小鼠血管内皮舒张功能的影响

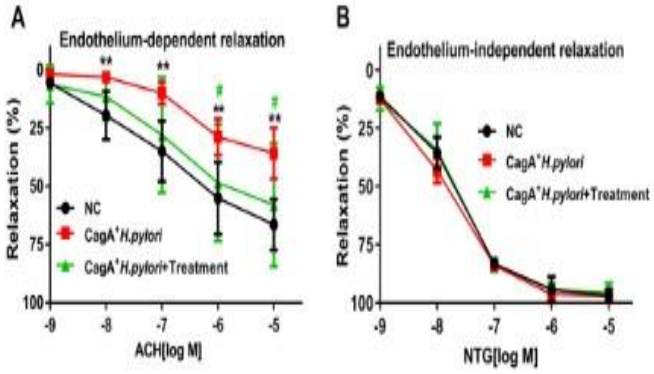


图4 抗Hp治疗对C57BL/6小鼠血管内皮舒张功能的影响

我们的研究

（3）外泌体抑制剂可部分恢复Hp感染小鼠受损的血管内皮舒张功能图6）。

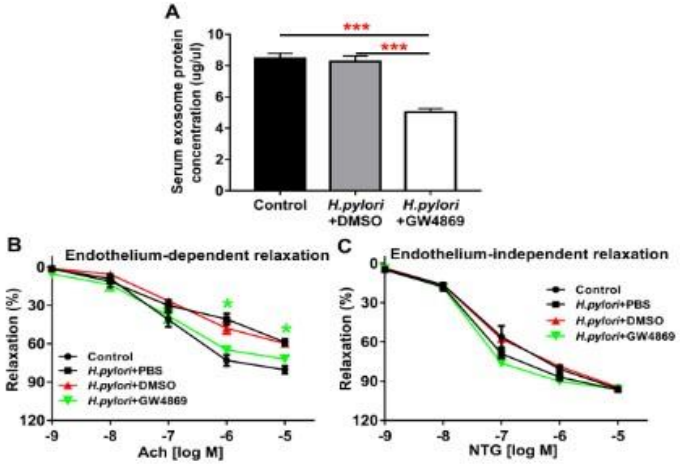


图5 外泌体抑制剂对CagA$^+$ Hp感染C57BL/6小鼠血管内皮舒张功能的影响

我们的研究

（4）含CagA的外泌体损伤血管内皮细胞功能

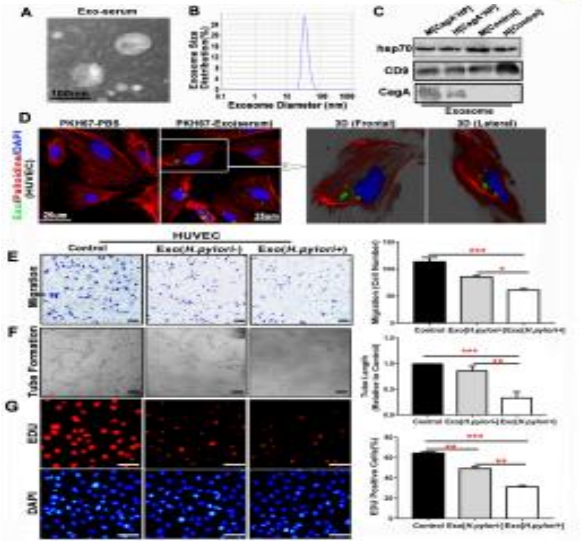


图6 外泌体的鉴定及其内化进入血管内皮细胞， Hp感染者外泌体对血管内皮细胞生物学功能的影响

Xia XJ, Zhang LF, Chi JS, Li H, Liu XM, Hu TZ, Li R, Guo YJ, Zhang X, Wang H, Cai J, Li YX, Liu D, Cui YQ, Zheng XL, Flaker GC, Liao DF, Hao H, Liu ZG *, **Xu CX*.** Helicobacter pylori Infection Impairs Endothelial Function Through an Exosome -Mediated Mechanism. J Am Heart Assoc, 2020 Mar 17;9(6):e014120. doi: 10.1161/JAHA.119.014120. Epub 2020 Mar 15. **（SCI收录，IF 4.605，JCR一区）**

小 结

- Hp感染是CAD和颈动脉粥样硬化的独立危险因素 并与早期冠脉硬化有关， 早期根除Hp冠心病的发生率呈下降的趋势 。
- Hp感染是冠心病患者死亡的独立预测因子,根除Hp能降低血管疾病的死亡率。
- Hp感染可能通过外泌体途径，激活血管炎症和免疫反应，损伤血管内皮功能，促进动脉粥样硬化等血管疾病的发生发展
- 关注Hp与血管疾病，防治Hp，以望减少血管疾病的发生。

Polaprezinc combined with clarithromycin based triple therapy for *Helicobacter pylori* associated gastritis: A prospective, multicenter, randomized clinical trial

Bei Tan[1], Han-Qing Luo[1*], Hong Xu[2], Nong-Hua Lv[3], Rui-Hua Shi[4], He-Sheng Luo[5], Jian Sheng Li[6], Jian-Lin Ren[7], Yi-You Zou[8], Yan-Qing Li[9], Feng Ji[10], Jing-Yuan Fang[11], Jia Ming Qian[1*]

The efficacy and safety of polaprezinc combined with triple therapy was compared with triple therapy alone in the eradication of *Helicobacter pylori*. A randomized, parallel-group, open label, controlled, prospective multicenter study was conducted in 11 cities in China. Treat ment-naive patients with *H. pylori*–associated gastritis were randomly assigned to one of three arms for a 14-day treatment: Arm A triple therapy (omeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg, each twice daily) plus polaprezinc 75 mg twice daily; Arm B triple therapy plus polaprezinc 150 mg twice daily, or Arm C triple therapy alone. The rate of *H. pylori* eradication was the primary endpoint. Secondary endpoints were symptom improvement and lower incidence of adverse events. 303 patients completed the study– 106, 96, and 101 patients in Arms A, B, and C, respectively.

Intention-to-treat (ITT) analysis showed that the rate of H. pylori eradication was significantly higher for Arms A (77.0%) and B (75.9%) compared to Arm C (58.6%) ($P < 0.01$), whereas there was no difference between Arms A and B ($P = 0.90$). Per-protocol (PP) analysis showed that the rate of H. pylori eradication was significantly higher for Arms A (81.1%) and B (83.3%) compared to Arm C (61.4%) ($P < 0.01$), whereas there was no significant difference between Arms A and B ($P = 0.62$). All three groups reported significant symptom improvement at 7, 14, and 28 days after treatment, compared to baseline ($P < 0.0001$). The adverse event rate for Arm B (5.1%) was higher than for Arms A (2.8%) ($P = 0.04$) and C (1.9%) ($P = 0.02$). There were no serious adverse events in ny group. It appears that standard dose polaprezinc combined with triple therapy can signifi cantly improve the H. pylori eradication rate, without an increase in toxicity.

Tan B, Luo H-Q, Xu H, Lv N-H, Shi R-H, Luo H-S, et al. (2017) Polaprezinc combined with clarithromycin-based triple therapy for Helicobacter pylori-associated gastritis: A prospective, multicenter, randomized clinical trial. PLoS ONE 12 (4): e0175625.

https://doi.org/10.1371/journal. pone.0175625

胃微生态与益生菌的应用

大连医科大学微生态学教研室

中国微生态学杂志编辑部

袁杰力

2021.11 长沙

胃微生态系统

- 人体微生态系统是指在一定结构的空间内, 人体正常微生物群以人体的组织、细胞及其代谢产物为环境形成的能独立的进行物质、能量及基因相互交流的统一的生物系统。
- 口腔微生态系统、消化道微生态系统、泌尿生殖道微生态系统、皮肤微生态系统、呼吸道微生态系统等。
- 胃微生态系统就是消化道微生态系统内的一个相对独立的微生态系统。由于胃内环境的特殊性，胃是消化道微生态系统中一个特别的区域。

胃内微生态研究史上的主要事件

时间	作者	事件	文献
1893年	Bizzozero等	在狗胃内发现螺旋状细菌	[1]
1906年	Krienitz等	在人胃内发现“螺旋体”微生物	[2]
1915年	Rosenow等	在消化性溃疡患者胃内发现“螺旋体”微生物	[5]
1921年	Luger等	证实胃癌患者胃内有“螺旋体”微生物存在，健康人则没有	[6]
1924年	Luck等	在狗胃内发现有尿素酶活性	[7]
1932年	Applmans等	在消化性溃疡和胃癌患者胃内同时发现了螺旋状微生物	[8]
1950年	Fitzgerald等	消化性溃疡病人胃内尿素酶产生的氨可以中和胃酸	[9]
1959年	Lieber等	用四环素治疗后的尿毒症病人胃内尿素酶活性降低	[10]
1968年	Delluva等	动物研究证实胃内尿素酶来源于细菌	[11]
1975年	Steer等	在80%胃溃疡切除标本上发现有细菌	[12]
1981年	Meshkinpour等	从胃液中分离培养出G-细菌和*Pseudomonas*	[14]
1981年	Lacent杂志	在溃疡患者胃液内可检测出大量具抗药性的细菌菌株，其中包括*Streptococcus, Neisseria*和*Lactobacillus*	[15]
1983年	Warren等	报道从胃粘膜上成功分离出细菌，即*H. pylori*	[16]
1988年	Sjöstedt等	胃液中分离培养出*Streptococci, Bifidobacteria/Lactobacilli, Micrococci/Staphylococci*	[17]
2000年	Monstein等	以TTGE法检测了胃黏膜微生物种类，发现*Enterococcus, Pseudomonas, Streptococcus, Staphylococcus*和*Stomatococcus*	[20]
2006年	Bik等	以16S rDNA测序法检测胃黏膜微生物，发现*Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes*和*Fusobacteria*门的细菌	[21]
2009年	Li等	16S rDNA测序结合qPCR法检测了胃黏膜菌群，发现胃内主要菌群为*Firmicutes*菌门及*Streptococcus*菌属	[22]
2009年	Dicksved等	以T-RFLP结合16S rDNA测序法分析了胃黏膜微生物，发现*Streptococcus, Lactobacillus, Veillonella*和*Prevotella*属的细菌	[23]
2011年	Stearns等	16S rDNA测序法发现胃黏膜主要存在*Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria*和SR1 5大菌门的微生物	[24]
2011年	Maldinado-Contreras等	焦磷酸测序法分析了幽门螺杆菌在胃内不同定植情况下对胃微生态的影响	[29]
2013年	von Rosenvinge等	以16S rDNA测序结合转录测序的方法发现胃液中的微生物包括*Firmicutes, Bacteroidetes, Fusobacteria, Actinobacteria, Proteobacteria*门的微生物	[26]
2014年	Eun等	以高通量测序技术比较了慢性胃炎、胃组织形变、及胃癌患者的胃黏膜菌群	[30]
2016年	Yang等	以高通量测序法比较了不同胃癌患病风险人群胃部微生态结构	[32]
2016年	Jo等	以焦磷酸测序法分析了胃癌患者胃内不同部位的黏膜组织，并未发现与胃癌直接相关的其它菌群（除*H. pylori*菌外的）	[33]

普遍认为健康人胃部没有微生物长期定植

- 胃酸的产生使胃内微环境pH值偏低，细菌难以存活；
- 胃黏液层的厚度和胃蠕动的有效性都可能阻碍细菌在胃内的定植
- 唾液和食物中所含的硝酸盐被乳酸菌还原成亚硝酸盐，这些物质都起到抗菌剂的作用。

H. pylori 感染导致胃黏膜慢性炎症机制的发现开启胃生态学研究新篇章

- 1984 年，Warren 和 Marshall 在胃内分离出一种革兰氏阴性菌，即幽门螺杆菌，揭开了H.pylori 与消化疾病研究的新纪元和获得了诺贝尔医学奖。
- 基于传统培养方法的研究证实胃内仍有大量耐酸菌种存在，主要是来源于口腔和食物的过路菌，含量一般在 10^3 CFU/mL 以下，种类有数百种之多。

胃内微生物群落结构

- 胃内占优势的细菌门水平主要为硬壁菌门、放线菌门、拟杆菌门、蛋白菌门和梭杆菌门；
- 培养和高通量测序方法证实优势菌属为：丙酸杆菌属、乳杆菌属、链球菌属和葡萄球菌属；
- 个体间胃内细菌差异较大；胃内微生物群落构成与口腔、咽喉部、鼻腔和肠道菌群构成也存在显著不同；
- 胃体和胃窦粘膜因酸性不同可能会导致不同的菌落定植，但研究表明这两个位置上的大部分菌群差别不大。
- 胃黏膜菌群总量高于胃液，而胃液中菌群多样性更高并且两者菌群结构存在明显差异。

Dietary intake of female bariatric patients after anti -obesity gastroplasty. Clinics (Sao Paulo) 2006, 61(2):93-98.

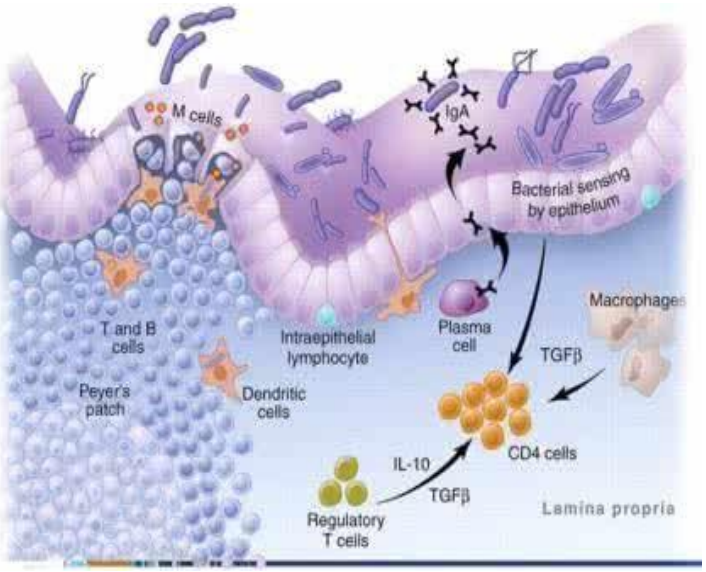
人体胃内菌群特征

优势菌种	标本类型	检测方法	参考文献
Gram-negative bacteria and *Pseudomonas*	抽吸物	培养	Meshkinpour et al. (1981)
Streptococci, Bifidobacteria/Lactobacilli, and *Micrococci/staphylococci*	抽吸物	培养	Sjostedt et al. (1988)
Enterococcus, Pseudomonas, Streptococcus, Staphylococcus, and *Stomatococcus*	粘膜	TTGE	Monstein et al. (2000)
Veillonella sp., Lactobacillus sp., and Clostridium sp.	抽吸物	培养	Dias et al. (2006)
Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes, and Fusobacteria phyla	粘膜	16S rDNA 测序	Bik et al. (2006)
Streptococcus, Lactobacillus, Veillonella, and Prevotella	粘膜	T-RFLP+16SrDNA 测序	Dicksved et al. (2009)
Firmicutes phylum and *Streptococcus* genus	粘膜	16S rDNA 测序+qPCR	Li et al. (2009)
Firmicutes, Proteobacteria, Bacterodetes, Actinobacteria, and *SR1* phylum	粘膜	16S rDNA 测序	Stearns (2011)

TTGE: 时相温度凝胶梯度电泳; T-RFLP:末端限制性片段长度多态性分析
qPCR: 定量聚合酶链反应

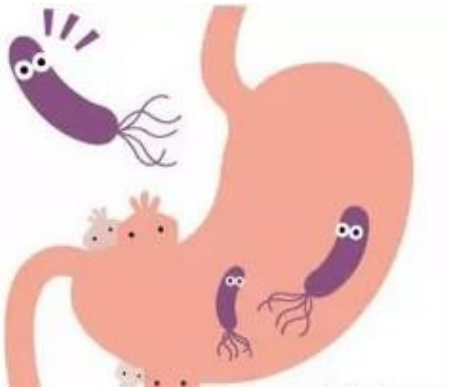
胃微生态的平衡对维持正常生理功能的作用

- 生物拮抗作用
- 免疫刺激作用
- 排毒作用
- 抗肿瘤作用



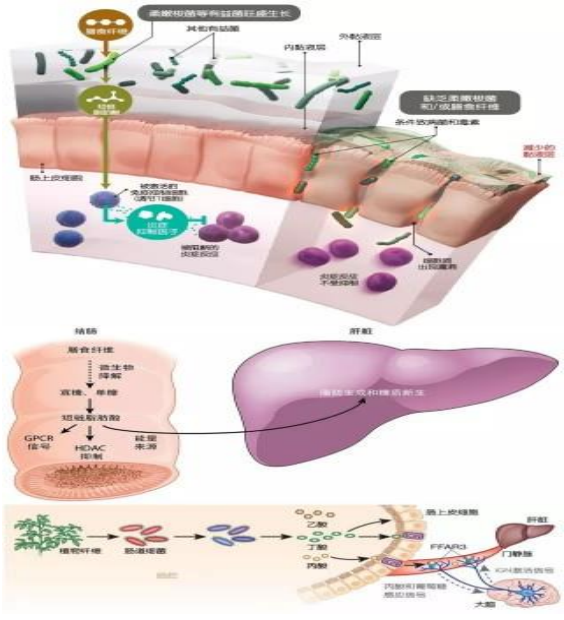
胃内微生物群的构成受诸多因素影响

- 口腔细菌的组成
- 胆汁反流
- 性别
- 年龄
- 药物
- *Hp*感染
- 饮食因素
- 疾病



饮食与胃内菌群

- 胃酸能杀灭食物中所含的大部分外来菌群，但仍有少部分菌能适应这个酸性环境，并能机会定植于胃或肠道中
- 随着饮食成分的改变，胃内菌群结构也发生相应改变
- 给予大鼠非纯化饮食后，其胃粘膜Lactobacilli水平要比纯化饮食大鼠要高，并且与TLR2 mRNA水平负相关。



Bioscience, biotechnology and biochemistry 2012, 76(9):1728 -1732.

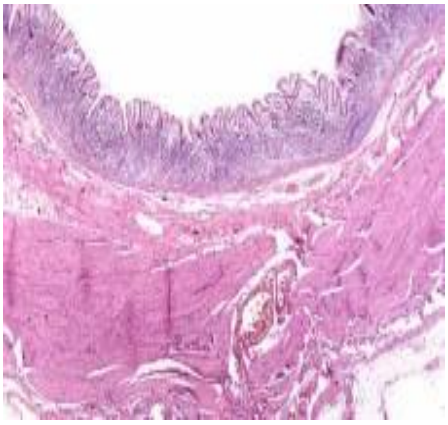
PPI与胃内菌群

- PPI可能存在着干扰菌群平衡和发生肠内感染和腹泻的风险
- 奥美拉唑能有效减少HP相对丰度，增加变形杆菌属 厚壁菌门和梭菌属的相对丰度。
- PPI使用者胃中pH 值升高，更易感染其它非HP菌落
- PPI使用导致 Lactobacilli 的减少，而酵母菌和其它真菌随之过度生长。

The Laryngoscope 2008, 118(4):599 -604.

萎缩性胃炎的胃内菌群

- 萎缩性胃炎病人较健康对照组链球菌属升高，普氏菌属数量下降；
- 萎缩性胃炎病人分泌胃酸的能力下降，使得胃内细菌总量升高；
- 细菌数量升高与胃内积聚亚硝酸盐的含量呈正相关。



Best Practice& Research Clinical Gastroenterology, 2013, 27(1): 39 -45.

H. pylori 对胃内细菌群落构成的影响

- *Hp*在胃内占绝对优势的样本中，非 *Hp*序列显著降低，而且菌群多样性降低；
- 螺旋体属和*Hp*间呈正相关，而拟杆菌门、绿弯菌门、蓝藻菌、梭菌属、浮微菌门、β-和γ-变形菌及疣微菌门和 *Hp*呈负相关；
- 也有研究认为胃内 *Hp*存在与否，以及胃内 pH值水平，对胃内菌群种群构成并无影响，但可能提高个体间胃内菌群的变异性。

*Hp*根除治疗与胃肠道微生态间的相互作用

- 标准的*Hp*根除治疗包括质子泵抑制剂和抗菌药物。抗菌药物的使用可引起敏感菌数量的减少、耐药菌的繁殖以及菌群数量和种类的失衡，质子泵抑制剂会引起胃内 pH值升高，从而进一步导致菌群失调；
- 接受*Hp*根除治疗时会出现一系列胃肠功能紊乱的症状 如腹胀、食欲不振、腹泻、便秘等；
- 补充益生菌可减少至根除治疗中抗生素引起的胃肠道菌群变化和失衡，避免肠道耐药菌的生长和提高 Hp根除率。

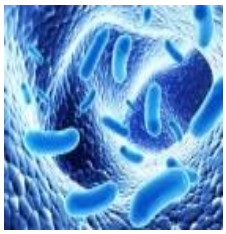
中国实用儿科杂志2016年8月 第31卷 第8期

乳杆菌对*Hp*的影响

- 乳杆菌属对*Hp*有明显的抑制作用，且抑制作用的效果与乳杆菌属相对浓度呈正相关；
- 乳杆菌抑制*Hp*尿素酶活性，*Hp*感染沙鼠模型进行灌胃后，乳杆菌菌株能在较短时间内(2周)清除沙鼠胃内*Hp*的定植，清除率达到60%左右；
- 单纯的乳杆菌灌胃治疗，并不能改善因*Hp*感染而破坏的胃内菌群结构。

宋阳.幽门螺杆菌感染对胃内菌群结构的影响和菌群分布特征的研究第三军医大学博士论文 2012.5

益生菌在*Hp*根治治疗中的作用地位



- 益生菌可通过稳定粘膜屏障，分泌多种抗菌物质，抑制 Hp粘附，抑制由*Hp*引起的炎症反应，增强宿主免疫屏障功能起到抗 Hp作用，防止其再定植；
- Meta分析报告：在根除疗法的基础上使用包含乳杆菌属的益生菌能明显提高成人和儿童 *Hp*根除率；
- 双歧杆菌、布拉氏酵母菌、混合益生菌也可明显提高 *Hp*根除率。

益生菌产生保护作用的机制

- 产生有机酸、过氧化氢、细菌素等抑制物，降低活菌数，并影响细菌代谢或毒素的产生；
- 竞争性抑制细菌与肠上皮细胞的结合位点与病原菌竞争营养物；
- 降解肠粘膜细胞上的毒素受体；
- 刺激宿主免疫反应 。

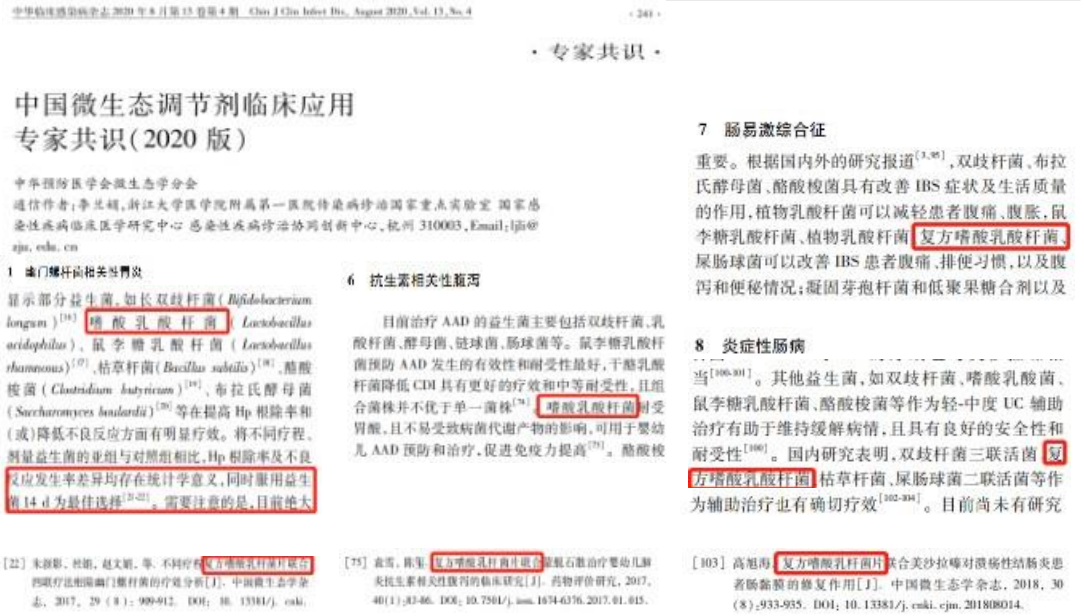
复方嗜酸乳杆菌制剂（益君康®）

由2株不同来源的嗜酸乳杆菌、粪链球菌及枯草杆菌组成的四联活菌制剂，用于肠道菌群失调引起的肠道功能紊乱。

列入2020版全国医保西药部分第177号，缓解消化道不适症状的复方OTC制剂。

复方嗜酸乳杆菌片循证支持（共识推荐）

2020版《中国微生态调节剂临床应用专家共识》推荐：复方嗜酸乳杆菌片可用于幽门螺杆菌相关性胃炎、抗生素相关性腹泻、肠易激综合征、炎症性肠病等应用。



· 专家共识 ·

中国微生态调节剂临床应用
专家共识(2020 版)

1 幽门螺杆菌相关性胃炎

显示部分益生菌，如长双歧杆菌(*Bifidobacterium longum*)[16]、嗜酸乳酸杆菌(*Lactobacillus acidophilus*)、鼠李糖乳酸杆菌(*Lactobacillus rhamnosus*)[17]、枯草杆菌(*Bacillus subtilis*)[18]、酪酸梭菌(*Clostridium butyricum*)[19]、布拉氏酵母菌(*Saccharomyces boulardii*)[20]等在提高 Hp 根除率和(或)降低不良反应方面有明显疗效。将不同疗程、剂量益生菌的亚组与对照组相比，Hp 根除率及不良反应发生率差异均存在统计学意义，同时服用益生菌 14 d 为最佳选择[21-22]。需要注意的是，目前绝大

6 抗生素相关性腹泻

目前治疗 AAD 的益生菌主要包括双歧杆菌、乳酸杆菌、酵母菌、链球菌、肠球菌等。鼠李糖乳酸杆菌预防 AAD 发生的有效性和耐受性最好，干酪乳酸杆菌降低 CDI 具有更好的疗效和中等耐受性，且组合菌株并不优于单一菌株[74]。嗜酸乳酸杆菌耐受胃酸，且不易受致病菌代谢产物的影响，可用于婴幼儿 AAD 预防和治疗，促进免疫力提高[75]。酪酸梭

7 肠易激综合征

重要。根据国内外的研究报道[3,95]，双歧杆菌、布拉氏酵母菌、酪酸梭菌具有改善 IBS 症状及生活质量的作用，植物乳酸杆菌可以减轻患者腹痛、腹胀，鼠李糖乳酸杆菌、植物乳酸杆菌、复方嗜酸乳酸杆菌、屎肠球菌可以改善 IBS 患者腹痛、排便习惯，以及腹泻和便秘情况；凝固芽孢杆菌和低聚果糖合剂以及

8 炎症性肠病

当[100-101]。其他益生菌，如双歧杆菌、嗜酸乳酸菌、鼠李糖乳酸杆菌、酪酸梭菌等作为轻-中度 UC 辅助治疗有助于维持缓解病情，且具有良好的安全性和耐受性[100]。国内研究表明，双歧杆菌三联活菌、复方嗜酸乳酸杆菌、枯草杆菌、屎肠球菌二联活菌等作为辅助治疗也有确切疗效[102-104]。目前尚未有研究

[22] 朱丽影，付娟，赵文娟，等. 不同疗程复方嗜酸乳杆菌片联合四联疗法根除幽门螺杆菌的疗效分析[J]. 中国微生态学杂志，2017，29(8)：909-912. DOI：10.13381/j.

[75] 袁雪，陈军. 复方嗜酸乳杆菌片联合蒙脱石散治疗婴幼儿肠炎抗生素相关性腹泻的临床研究[J]. 药物评价研究，2017，40(1)：63-66. DOI：10.7501/j.issn.1674-6376.2017.01.015.

[103] 高旭海. 复方嗜酸乳杆菌片联合美沙拉嗪对溃疡性结肠炎患者肠黏膜的修复作用[J]. 中国微生态学杂志，2018，30(8)：933-935. DOI：10.13381/j.cnki.cjm.201808014.

中国微生态调节剂临床应用专家共识(2020版)[J]. 中华临床感染病杂志2020，13(4)：241-256.

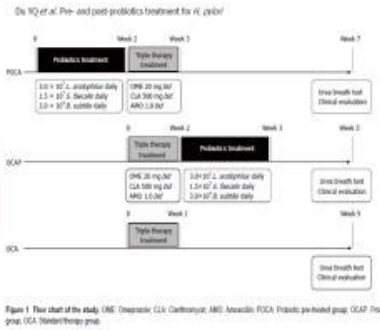
复方嗜酸乳杆菌片对*Hp*治疗的应用

复方嗜酸乳杆菌片联合三联疗法治疗Hp 感染的随机、对照、多中心临床研究，证实在三联治疗前或三联治疗结束后应用 2周益生菌，可提高HP根除率，且副作用低安全性好。

- 研究单位：上海长海医院，上海交通大学新华医院，上海同济大学同济医院，上海市第一人民医院等7家医疗机构；
- 研究目的：观察复方嗜酸乳杆菌片联合奥美拉唑三联疗法根除幽门螺杆菌的疗效，比较不同阶段益生菌辅助治疗与单纯三联疗法在Hp根除率和不良反应发生率上的差异，探讨其作为Hp根除治疗的临床价值。

World Journal of Gastroenterology

Adjuvant probiotics improve the eradication effect of triple therapy for *Helicobacter pylori* infection



Du YQ et al. Pre- and post-probiotics treatment for *H. pylori*

Figure 1 Flow chart of the study. OME: Omeprazole; CLA: Clarithromycin; AMO: Amoxicillin; POCA: Probiotic pre-treated group; OCAP: Probiotic post-treated group; OCA: Standard therapy group.

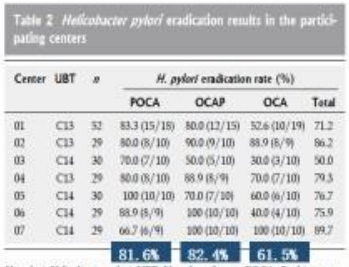


Table 2 *Helicobacter pylori* eradication results in the participating centers

Center	UBT	*n*	*H. pylori* eradication rate (%)			
			POCA	OCAP	OCA	Total
01	C13	52	83.3 (15/18)	80.0 (12/15)	52.6 (10/19)	71.2
02	C13	29	80.0 (8/10)	90.0 (9/10)	88.9 (8/9)	86.2
03	C14	30	70.0 (7/10)	50.0 (5/10)	30.0 (3/10)	50.0
04	C13	29	80.0 (8/10)	88.9 (8/9)	70.0 (7/10)	79.3
05	C14	30	100 (10/10)	70.0 (7/10)	60.0 (6/10)	76.7
06	C14	29	88.9 (8/9)	100 (10/10)	40.0 (4/10)	75.9
07	C14	29	66.7 (6/9)	100 (10/10)	100 (10/10)	89.7
			81.6%	82.4%	61.5%	

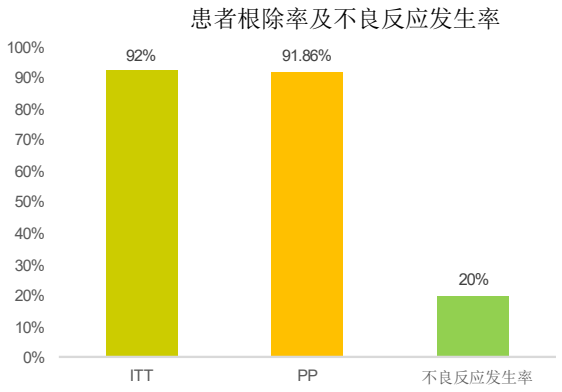
H. pylori: *Helicobacter pylori*; UBT: Urea breath test; POCA: Probiotic pre-treated group; OCAP: Probiotic post-treated group; OCA: Standard therapy group.

无论在开始OCA三联治疗前或于三联治疗结束后应用2周益生菌治疗，均可显著提高OCA方案Hp根除率，且副作用低、安全性好，有较高的临床应用价值。

Du YQ, et al. World J Gastroenterol 2012, 18(40): 63

复方嗜酸乳杆菌片对*Hp*治疗的应用

复方嗜酸乳杆菌联合含四环素和呋喃唑酮四联方案作为幽门螺杆菌感染的补救疗法 ，证实对于多次根除幽门螺杆菌失败的患者，可尝试先服用复方嗜酸乳杆菌片 2周，再用含四环素和呋喃唑酮的四联疗法，不仅可以降低患者不良反应，且可以提高根除率。



研究方法：至少2次Hp根除失败患者。d1-14: 复方嗜酸乳杆菌(1g tid)；d15-24：四环素、呋喃唑酮四联补救（埃索美拉唑[20mg bid] +枸橼酸铋钾[220mg bid] +四环素[750mg bid] +呋喃唑酮[100mg bid])

Airu Liu, Yuxin Wang, Yingxiao Song, and Yiqi Du. Saudi J Gastroenterol. 2020 Mar-Apr; 26(2): 78 – 83.

复方嗜酸乳杆菌片对*Hp*治疗的应用）

2017年WGO益生菌指南推荐部分益生菌应用于Hp根除，复方嗜酸乳杆菌片被指南推荐在一线治疗方案中提高 Hp根除率的益生菌

2017年2月，世界胃肠病学组织(WGO)更新发布了《益生菌和益生元》全球指南，值得注意的是，基于在Hp根除中的循证证据，益君康®是唯一被推荐在一线治疗方案中提高Hp根除率的微生态制剂。

Helicobacter pylori (HP)					
Coadjuvant therapy for HP eradication	*Lactobacillus rhamnosus* GG	6×10^9 twice daily	2	[7]	Reduction in therapy-related side effects in first line therapy
	Bifidobacterium animalis subsp. *lactis* (DSM15954), *Lactobacillus rhamnosus* GG	10^9–10^{10} living bacteria twice daily	2	[21]	Reduction in therapy-related side effects
	Lactobacillus reuteri DSM 17938	1×10^8, CFU three times daily	2	[22]	Reduction in therapy-related side effects in levofloxacin second-line therapy
	Mixture of *Lactobacillus acidophilus* and *L. bulgaricus* and *Bifidobacterium bifidum* and *Streptococcus thermophilus* and galacto-oligosaccharides	$5 \times 10^9 + 1 \times 10^9$, live cells twice daily	2	[23]	Improves treatment compliance in sequential therapy
	Lactobacillus acidophilus, *Streptococcus faecalis*, *Bacillus subtilis*	5×10^8, 2.5×10^8, 5×10^7	3	[24]	Improves eradication rates in first-line therapy
	Saccharomyces boulardii CNCM I-745	10^9 CFU/capsule of 250 mg, twice daily	2	[7]	Reduction in therapy-related side effects
	Kefir	250 mL twice daily	3	[25]	
	Bacillus clausii (Enterogermina strains)	2×10^9 spores, three times daily	2	[26]	

World Gastroenterology Organisation Global Guidelines Probiotics and prebiotics February 2017 .

联合蒙脱石散对抗生素相关性腹泻的治疗

复方嗜酸乳杆菌片 结合蒙脱石散治疗婴幼儿肺炎抗生素相关性腹泻，总有效率可达93.55%，缩短患儿临床症状消失时间，提高免疫功能，降低 DAO水平，疗效确切。

- 研究目的：探讨复方嗜酸乳杆菌片结合蒙脱石散治疗婴幼儿肺炎抗生素相关性腹泻的效果及对免疫功能的影响。
- 研究方法： 62例婴幼儿肺炎抗生素相关性腹泻患儿，按照随机数字法分为两组（n=31），对照组患儿予以蒙脱石散口服进行治疗，研究组患儿予以复方嗜酸乳杆菌片结合蒙脱石散口服进行治疗。

表 2 症状缓解时间比较（$\bar{X}$±SD，n=31）

组别	退热时间（天）	纠正脱水时间（天）	止泻时间（天）
研究组	1.76±0.25*	1.92±0.25*	3.34±0.26*
对照组	2.99±0.36	2.65±0.41	4.51±0.38

注：与对照组相比，*P<0.05。

表 3 免疫功能指标 DAO 水平比较（X±SD，n=31）

组别	时间	IgG（g·L^{-1}）	IgA（g·L^{-1}）	CD4+（%）	CD3+（%）	CD8+（%）	CD4+/CD8+	DAO（μ·mL^{-1}）
研究	干预前	6.68±0.19	1.46±0.31	28.61±3.93	44.51±4.97	21.31±2.61	0.81±0.36	53.21±4.69
组	干预后	9.78±1.97#*	1.68±0.22#*	36.61±3.74#*	52.69±5.97#*	28.64±2.28#*	1.59±0.61#*	13.51±1.79#*
对照	干预前	6.67±0.58	1.44±0.19	28.64±3.49	44.78±4.61	21.36±2.61	0.82±0.63	52.13±4.17
组	干预后	6.70±0.59#	1.46±0.19#	29.64±2.79#	45.97±4.61#	24.13±2.97#	0.83±0.49#	18.63±2.19#

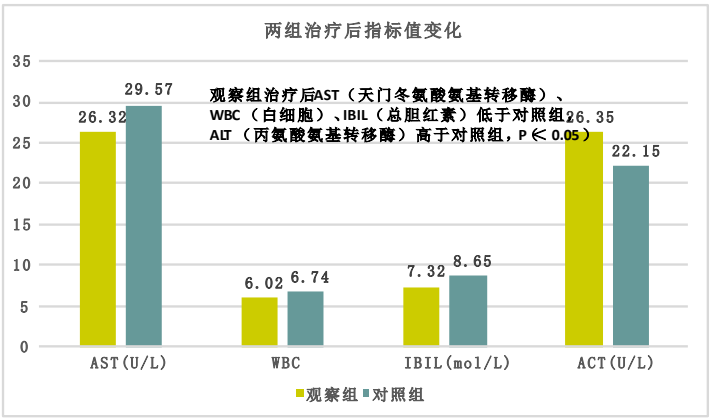
注：与对照组相比，*P<0.05；与干预前相比，#P<0.05。

裴雪霞. 复方嗜酸乳杆菌片结合蒙脱石散治疗婴幼儿肺炎抗生素相关性腹泻的效果及对免疫功能的影响[J]，四川生理科学杂志，2020，42(2)

联合复方谷氨酰胺对炎症性肠病的治疗

复方嗜酸乳杆菌片联合复方谷氨酰胺治疗 炎症性肠病菌群失调患者，效果显著，临床应用价值较高。

- 研究目的：观察复方谷氨酰胺联合嗜酸乳杆菌治疗炎症性肠病菌群失调的临床效果。
- 试验方法： 80 例炎症性肠病菌群失调患者，随机分为观察组（40 例）和对照组（40 例）。观察组采用复方谷氨酰胺联合复方嗜酸乳杆菌片治疗，对照组采用复方谷氨酰胺治疗。



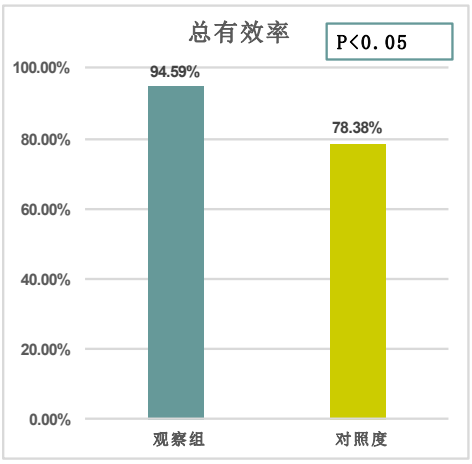
评估指标：使用静脉血查看患者天门冬氨酸氨基转（AST）、白细胞（WBC）、总胆红素（IBIL）、丙氨酸氨基转移酶（ALT）变化。

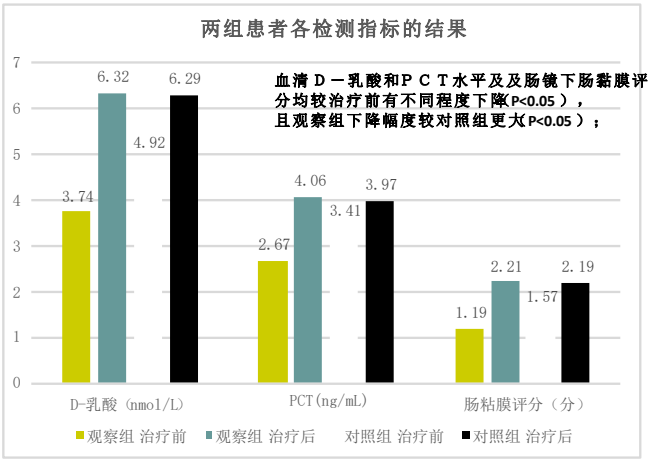
贾殿萍. 复方谷氨酰胺联合嗜酸乳杆菌治疗炎症性肠病菌群失调的效果分析[J]，医药前言，2019年9月第9卷第27期

联合美沙拉嗪缓释颗粒对UC的治疗

复方嗜酸乳杆菌片联合美沙拉嗪缓释颗粒对UC的治疗可明显减轻患者肠黏膜病变程度，保护肠黏膜屏障，加快其修复。

- 研究目的：探讨复方嗜酸乳杆菌片联合美沙拉嗪缓释颗粒对溃疡性结肠炎患者肠黏膜的修复作用。
- 研究方法：活动期UC患者，随机分为观察组和对照组各37例。两组患者均给予相同的饮食指导及营养支持治疗。对照组患者给予美沙拉嗪缓释颗粒。观察组在对照组基础上加用复方嗜酸**乳杆菌片。**



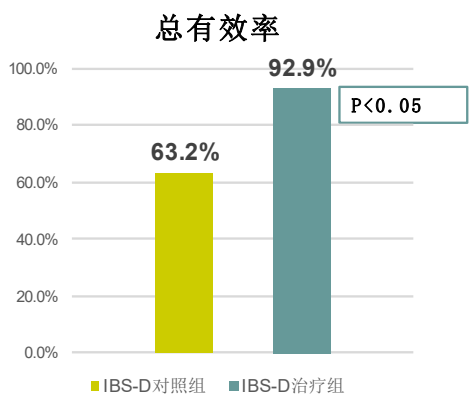


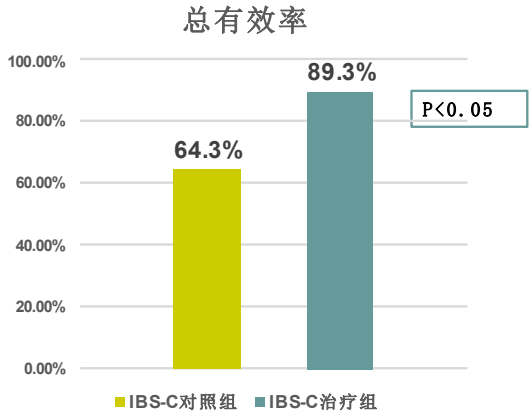
高旭海．复方嗜酸乳杆菌片联合美沙拉嗪对溃疡性结肠炎患者肠黏膜的修复作用[J]．中国微生态学杂志，2018,30（8）933-935.

联合胃肠动力药治疗IBS

复方嗜酸乳杆菌片联合胃肠动力药治疗 IBS患者，效果优于单用胃肠动力药。

- 研究目的：探讨复方嗜酸乳杆菌片对肠易激综合征(IBS)患者的治疗效果。
- 研究方法：IBS-D治疗组应用复方嗜酸乳杆菌片联合应用匹维溴铵进行治疗， IBS-D对照组单纯应用匹维溴铵治疗。IBS-C治疗组患者应用复方嗜酸乳杆菌片联合莫沙必利进行治疗， IBS-C 对照组单纯应用莫沙必利治疗。



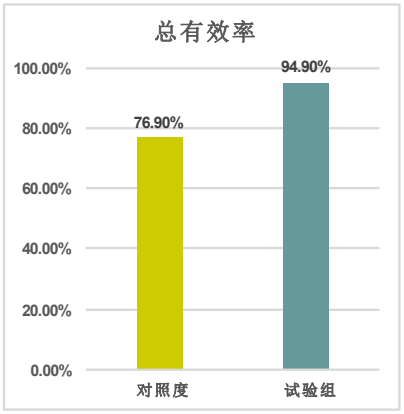


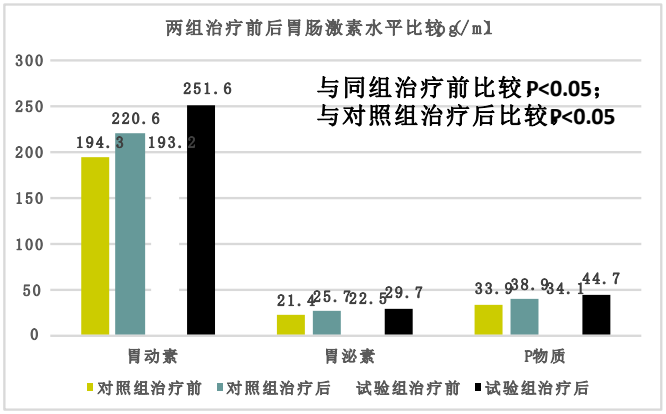
张鸣鸣，王华，程秋实．复方嗜酸乳杆菌片对肠易激综合征患者的疗效[J]．中国微生态学杂志，2018，30(11):52-54.

联合多潘立酮治疗功能性消化不良

复方嗜酸乳杆菌片联合多潘立酮治疗[1]功能性消化不良患者疗效显著，能有效缓解患者临床症状及体征，利于促进胃排空，调节胃肠激素，改善胃肠道动力。

- 研究目的：研究复方嗜酸乳杆菌片联合多潘立酮治疗功能性消化不良患者的临床疗效及对胃肠激素的影响。
- 研究方法：78 例功能性消化不良患者随机分为对照组与试验组，各39 例。对照组应用多潘立酮治疗，试验组应用复方嗜酸乳杆菌片联合多潘立酮治疗。





康志清．复方嗜酸乳杆菌片联合多潘立酮治疗功能性消化不良患者的临床疗效及对胃肠激素的影响[J]．医疗装备，2018，31（19 ）

复方嗜酸乳杆菌片优势

四菌协同

本品是由中国株嗜酸乳杆菌，日本株嗜酸乳杆菌、粪链球菌和枯草杆菌等四种菌粉组成，通过补充、占位、夺氧多重功效，达到调整肠道菌群失调的作用。

胃肠同治

本品中所含嗜酸乳杆菌作用人体的胃、小肠中，粪链球菌作用在人体的小肠、大肠中，枯草杆菌作用在结肠中，四菌协同，对胃、肠相关疾病均有治疗。

无需冷藏

益君康的四联活菌在常温下均不会失活，可以保证益君康的疗效。对医院药库、药房，可以减少低温贮存药物的额外支出。对患者，不但方便携带，而且药物疗效有保证。

循证支持

截至2021年6月，共收集到益君康相关文献400篇涉及250家以上等级医院，经多中心、权威认证，本品安全有效，值得临床推广应用。

国内外共识、指南、路径

2015年， 美国《益生菌防治溃疡性结肠炎缓解、 预防结肠储袋炎 共识》

2013年， 欧洲《益生菌治疗下消化道病症指南》

2012年，《炎症性肠病诊断与治疗的共识意见》

2010年，《便秘外科诊治专家共识》

2009年，《肠道菌群失调诊断治疗建议 》

2008年，《肠易激综合征诊断和治疗的共识意见 》

2011年，《肠易激综合症中西医结合诊疗共识意见 》

2009年，《儿童腹泻病诊断治疗原则的专家共识 》

2016年，《中国消化道微生态调节剂临床应用共识 》

2010年，《新生儿黄疸诊疗原则的专家共识 》

2009年，《婴儿过敏性疾病预防、诊断和治疗专家共识 》

2017年 国家卫计委发布的1010种临床路径中，有50余种疾病建议用微生态制剂进行治疗。

幽门螺杆菌感染个体化治疗的三项临床研究汇报

潘杰 温州市中心医院 消化内科 2021.11.13 长沙

我国幽门螺杆菌感染根除治疗的现状

“三高一低”

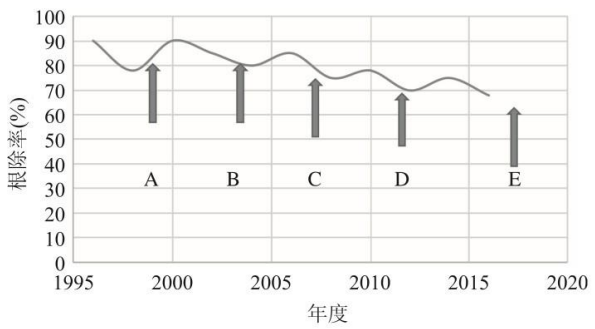
- 高人群感染率
- 高疾病负担
- 高耐药率
- 低根除率

胃肠病学和肝病学杂志 2017 年 6 月第 26 卷第 6 期 Chin J Gastroenterol Hepatol, Jun 2017, Vol. 26, No. 6 · 637 ·
doi:10.3969/j.issn.1006-5709.2017.06.005

述评

中国幽门螺杆菌治疗低根除率现状及应对策略

张建中
中国疾病预防控制中心传染病预防控制所,传染病预防控制国家重点实验室,感染性疾病协同创新中心,北京 102206



注:A、B、C、D、E 分别代表第一、二、三、四、五次全国幽门螺杆感染处理共识的发布时间点。

图 1 30 年间中国 *H. pylori* 根除方案变迁及经验治疗根除率变化示意图

幽门螺杆菌感染根除的相关方案

- 传统铋剂四联疗法： （PPI+ 铋剂 + 甲硝唑 + 四环素，PBMT）
- 不含铋剂的四联疗法：（伴随疗法-CT：PPI+ 阿莫西林 + 甲硝唑 + 克拉霉素，PAMC；序贯疗法-ST：PPI+ 阿莫西林，PA；序贯 PPI+ 甲硝唑 + 克拉霉素，PMC；混合疗法-HT；逆序贯疗法）
- 三联疗法： （PPI+ 阿莫西林 + 克拉霉素，PAC； PPI+ 甲硝唑 + 克拉霉素，PMC；PPI+ 阿莫西林 + 甲硝唑，PAM）以及包含喹诺酮的方案（PPI+ 阿莫西林 + 左氧氟沙星，PAL）

Therapeutic Advances in Gastroenterology *Review*

The status and progress of first-line treatment against *Helicobacter pylori* infection: a review

Caiqi Liu, Yuan Wang, Jiaqi Shi, Chunhui Zhang, Jianhua Nie, Shun Li and Tongsen Zheng

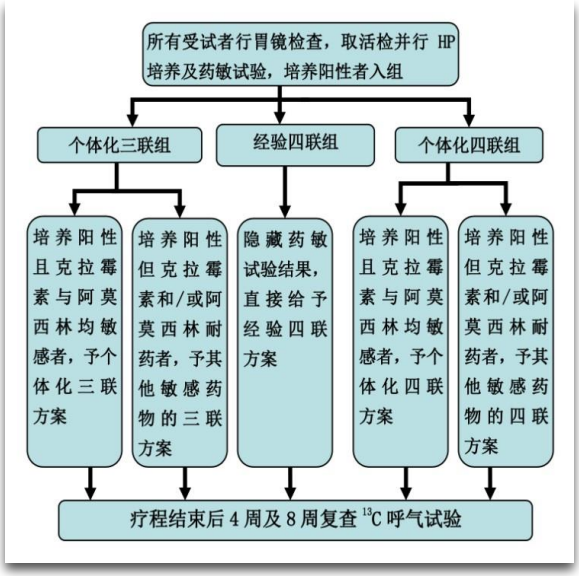
Ther Adv Gastroenterol
2021, Vol. 14: 1–12
DOI: 10.1177/1756284821989177

幽门螺杆菌感染一线治疗的现状与进展

- 随着HP对克拉霉素、甲硝唑、左氧氟沙星的耐药率不断提高，根除率下降，一些指南推荐的主流方案的效果可能不再令人满意。
- 指南：为提高一线治疗的根除率个体化治疗方案是首选（药敏试验），既能提供满意的根除率，又能防止抗生素滥用，避免全球抗生素耐药性进一步增加。但是，现实很骨干。（药敏试验的成本、难度和可获得性，个体化治疗难以实施）
- 在实践中，指南一致推荐使用BCQT为一线方案（经验性），伴随疗法(CT)也可用于无铋或克拉霉素高耐药的地区。
- PPI的三联疗法只能在耐药较低的地区使用。

个体化方案对幽门螺杆菌根除治疗的多中心RCT研究

个体化方案对幽门螺杆菌根除治疗的多中心 RCT研究(ChiCTR-TRC-13004223)



病例报告表（CRF）　（患者序号：　随机号：　）

姓名		性别		年龄		职业	
地址				联系方式			

此次就诊的主要症状（可多选）：□腹痛 □腹胀、早饱 □反酸、嗳气 □烧心、胸痛 □恶心、呕吐 □呕血 □黑便 其他

胃镜诊断结果（可多选）：□食管炎 □慢性浅表胃炎 □慢性萎缩性胃炎 □胃、十二指肠溃疡 其他

幽门螺杆菌根除治疗过程中出现的不适症状（可多选）：□腹痛 □腹胀 □恶心、呕吐 □腹泻 □皮疹 □便秘 □解黑褐色大便 □味觉失调 其他

病理结果

HP药敏试验结果		治疗药物选择	
克拉霉素	□敏感 □耐药	□ 雷贝拉唑	每次 10mg 一天2次（餐前半小时）
阿莫西林	□敏感 □耐药	□ 埃索美拉唑	每次 20mg 一天2次（餐前半小时）
左氧氟沙星	□敏感 □耐药	□ 枸橼酸铋钾	每次220mg 一天2次（餐前半小时）
呋喃唑酮	□敏感 □耐药	□ 胶体果胶铋	每次200mg 一天2次（餐前半小时）
甲硝唑	□敏感 □耐药	□ 克拉霉素	每次500mg 一天2次（餐后即服）
四环素	□敏感 □耐药	□ 阿莫西林	每次1000mg 一天2次（餐后即服）
其 它	□敏感 □耐药	□ 左氧氟沙星	每次500mg 一天1次（餐后即服）
		□ 左氧氟沙星	每次200mg 一天2次（餐后即服）
		□ 呋喃唑酮	每次100mg 一天2次（餐后即服）
		□ 甲硝唑	每次400mg 一天2次（餐后即服）
		□ 四环素	每次400mg 一天2次（餐后即服）

□ 经验四联 □ 个体化三联 □ 个体化四联			治疗开始时间
呼气试验	治疗前	□阳性 □阴性	
	治疗后4周	□阳性 □阴性	
	治疗后8周	□阳性 □阴性	

记录者：

Front. Med.
https://doi.org/10.1007/s11684-019-0706-8

RESEARCH ARTICLE

Is tailored therapy based on antibiotic susceptibility effective ? a multicenter, open-label, randomized trial

Jie Pan[1], Zhengchao Shi[2], Dingsai Lin[3], Ningmin Yang[4], Fei Meng[4], Lang Lin[5], Zhencheng Jin[6], Qingjie Zhou[1], Jiansheng Wu[7], Jianzhong Zhang (✉)[8,9], Youming Li (✉)[10]

[1]Wenzhou Central Hospital, Wenzhou 325000, China; [2]The People's Hospital of Ruian, Wenzhou 325200, China; [3]The Second People's Hospital of Cangnan, Wenzhou 325802, China; [4]Zhiyuan Inspection Medical Institute, Hangzhou 310009, China; [5]The First People's Hospital of Cangnan, Wenzhou 325800, China; [6]The First People's Hospital of Pingyang, Wenzhou 325400, China; [7]The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China; [8]State Key Laboratory of Infectious Disease Prevention and Control, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Chinese Center for Disease Control and Prevention, Beijing 102206, China; [9]National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China; [10]The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China

Abstract **An effective eradication therapy of *Helicobacter pylori* (*H. pylori*) should be used for the first time. In this study, we assessed whether tailored therapy based on antibiotic susceptibility testing is more effective than traditional therapy. We also evaluated the factors that cause treatment failure in high-resistance areas. For this multicenter trial, we recruited 467 *H. pylori*-positive patients. The patients were randomly assigned to receive tailored triple therapy (TATT), tailored bismuth-containing quadruple therapy (TABQT), or traditional bismuth-containing quadruple therapy (TRBQT). For the TATT and TABQT groups, antibiotic selection proceeded via susceptibility testing using an agar-dilution test. The patients in the TRBQT group were given amoxicillin, clarithromycin, esomeprazole, and bismuth. Successful eradication was defined as a negative ^{13}C-urea breath test at least eight weeks after the treatment ended. Susceptibility testing was conducted using an agar-dilution test. The eradication rate was examined via intention-to-treat (ITT) and per-protocol (PP) analyses. The clarithromycin, levofloxacin, and metronidazole resistance rates were 26.12%, 28.69%, and 96.79%, respectively. Resistance against amoxicillin and furazolidone was rare. The eradication rates for TATT, TRBQT, and TABQT were 67.32%, 63.69%, and 85.99% in the ITT analysis ($P < 0.001$) and 74.64%, 68.49%, and 91.22% in the PP analysis ($P < 0.001$), respectively. The efficacy of TABQT was affected by clarithromycin resistance, and bismuth exerted a direct influence on TATT failure. TABQT was the most efficacious regimen for use in high-resistance regions, especially among clarithromycin-susceptible patients.**

Keywords tailored triple therapy; tailored bismuth-containing quadruple therapy; traditional bismuth-containing quadruple therapy; antibiotic susceptibility testing; eradication rates

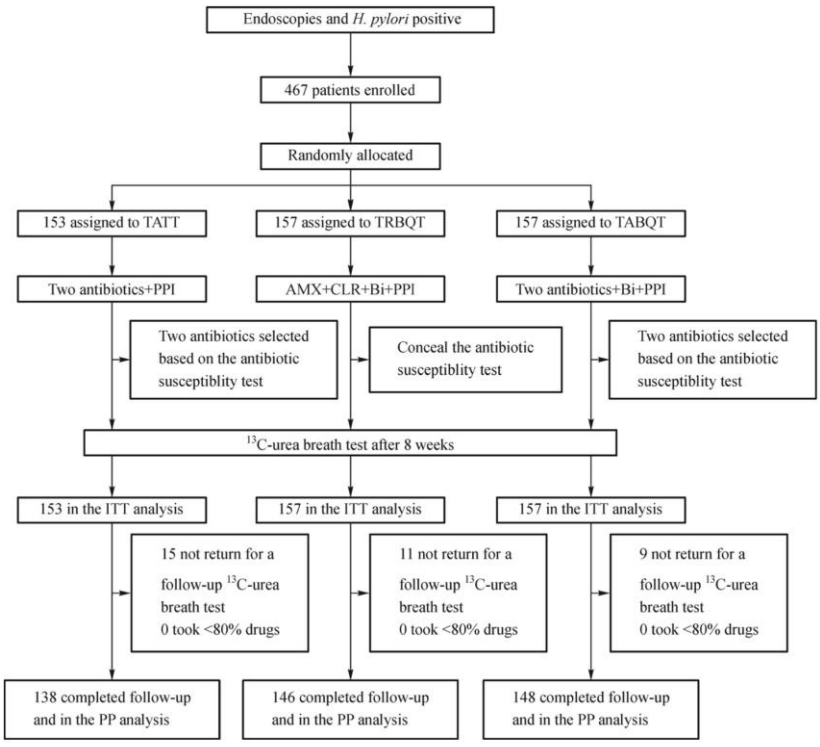


Fig. 1 Trial profile of the study. AMX, amoxicillin; Bi, bismuth; CLR, clarithromycin; ITT, intention-to-treat analysis; PP, per-protocol analysis; PPI, proton pump inhibitors; TABQT, tailored bismuth-containing quadruple therapy; TATT, tailored triple therapy; TRBQT, traditional bismuth-containing quadruple therapy.

Table 1 Demographic characteristics of patients and prevalence of antibiotic resistance

	TATT (n = 153)	TRBQT (n = 157)	TABQT (n = 157)	P value
Patient information				
Gender (M/F)	74/79	75/82	84/73	0.537
Age (year, mean, S.D.)	48.10 (11.41)	49.52 (11.88)	49.30 (10.25)	0.492
Pathological diagnosis				
Chronic gastritis	36.6% (56/153)	38.85% (61/157)	38.22% (60/157)	0.915
Chronic gastritis with intestinal metaplasia	18.95% (29/153)	23.57% (37/157)	19.11% (30/157)	0.519
Chronic gastritis accompanied with erosion	14.38% (22/153)	10.19% (16/157)	13.38% (21/157)	0.509
Chronic atrophy gastritis	16.7% (26/153)	15.92% (25/157)	19.74% (31/157)	0.656
Gastric mucosal atypical hyperplasia	11.11% (17/153)	9.55% (15/157)	7% (11/157)	0.45
Other	1.96% (3/153)	1.91% (3/157)	2.55% (4/157)	0.911
Antibiotic resistance rate				
CLR	29.41% (45/153)	21.02% (33/157)	28.03% (44/157)	0.195
LVX	30.72% (47/153)	24.84% (39/157)	30.57% (48/157)	0.424
MTZ	95.42% (146/153)	97.45% (153/157)	97.45% (153/157)	0.507
AMX	0% (0/153)	0% (0/157)	0% (0/157)	
FR	0% (0/153)	0% (0/157)	0% (0/157)	

AMX, amoxicillin; CLR, clarithromycin; F, female; FR, furazolidone; LVX, levofloxacin; M, male; MTZ, metronidazole; S.D., standard deviation; TABQT, tailored bismuth-containing quadruple therapy; TATT, tailored triple therapy; TRBQT, traditional bismuth-containing quadruple therapy.

Table 2 *H. pylori* eradication rates and side effects in the three treatments

Outcomes	TATT	TRBQT	TABQT
Eradication rate			
ITT analysis (%, *n*/*N*)	67.32% (103/153)*	63.69% (100/157)*	85.99% (135/157)
PP analysis (%, *n*/*N*)	74.64% (103/138) *	68.49%(100/146)*	91.22% (135/148)
Lost to follow-up evaluation (%, *n*/*N*)	9.8% (15/153)	7.01% (11/157)	5.73% (9/157)
Side effects (%, *n*/*N*)			
Abdominal pain	3.27% (5/153)	3.82% (6/157)	3.18% (5/157)
Bloating	3.92% (6/153)	9.55% (15/157)*	2.55% (4/157)
Nausea and vomiting	3.92% (6/153)	8.92% (14/157)	3.82% (6/157)
Diarrhea	6.53% (10/153)	7.64% (12/157)	6.37% (10/157)
Skin rash	2.61% (4/153)	2.55% (4/157)	3.82% (6/157)
Constipation	3.92% (6/153)	3.18% (5/157)	3.18% (5/157)
Black stool	0.65% (1/153)	0% (0/157)	0% (0/157)
Taste distortion	3.27% (5/153)	1.91% (3/157)	3.18% (5/157)

ITT, intention-to-treat analysis; PP, per-protocol analysis; TABQT, tailored bismuth-containing quadruple therapy; TATT, tailored triple therapy; TRBQT, traditional bismuth-containing quadruple therapy.
* indicates significant differences between TATT and TABQT (P<0.05) and between TRBQT and TABQT (P<0.05).

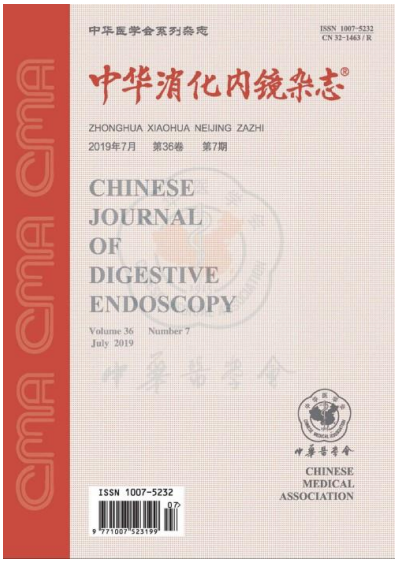
Table 3 *H. pylori* eradication rates of sensitive antibiotic selection in TATT and TABQT treatments

Antibiotic selection	AMX + CLR	AMX + LVX	AMX + FR
TATT			
ITT analysis (%, *n*/*N*)	68.52% (74/108)	76.19% (16/21)	54.17% (13/24)
PP analysis (%, *n*/*N*)	76.29% (74/97)	80% (16/20)	61.9% (13/21)
TABQT			
ITT analysis (%, *n*/*N*)	87.61% (99/113)*	80% (20/25)	84.21% (16/19)*
PP analysis (%, *n*/*N*)	93.4% (99/106) *	86.96% (20/23)	84.21% (16/19)

AMX, amoxicillin; CLR, clarithromycin; FR, furazolidone; ITT, intention-to-treat analysis; LVX, levofloxacin; PP, per-protocol analysis; TABQT, tailored bismuth-containing quadruple therapy; TATT, tailored triple therapy.
* indicates significant differences between the treatment of AMX + CLR from TATT and TABQT (P<0.05) and between the treatment of AMX + FR from TATT and TABQT (P<0.05).

个体化方案对幽门螺杆菌根除治疗的多中心RCT研究

- 结果：1、TABQT（个体）比TRBQT（经验）更有效；2、在抗生素高耐药性地区，铋剂非常必要，没有铋，TATT（个体三联）的根除率仍然很低；3、TATT与TRBQT的根除率无显著差异。
- HP治疗应基于区域耐药背景和耐药数据，结合药敏试验指导下的针对性治疗，从安全用药和经济产出比的角度出发。综上所述，根据药敏试验，TABQT患者的HP根除率较高。该方案对克拉霉素敏感患者有效。高耐药地区应选择铋剂。
- 从不良反应的角度来看，呋喃唑酮具有显著的遗传毒性、肝毒性和致癌性。因此，我们并不完全推荐含呋喃唑酮铋的四联疗法做为首选方案，因为在克拉霉素敏感患者TABQT方案的根除率为93.4%（PP分析）。



中华消化内镜杂志 2016 年 11 月第 33 卷第 11 期 Chin J Dig Endosc, November 2016, Vol. 33, No.11

·论著·

【专家点评】 幽门螺杆菌(*HP*)感染早在上世纪就被 WHO 定为胃癌的一级致癌因子,根除 *HP* 在一定程度上可预防和减少胃癌的发生。理想的根除 *HP* 的治疗方案是其根除率达到 90%以上,由于抗生素的耐药产生,在 *HP* 高耐药地区盲目采用指南推荐的根除四联方案,*HP* 的根除率常低于 80%。"幽门螺杆菌高耐药地区基于人群耐药背景的幽门螺杆菌根除方案效果评价"文章采用前瞻队列研究的方法,将 *HP* 感染者根据耐药培养结果分为阳性和阴性组,其中 187 例培养阳性者采用个体化治疗方案,培养阴性者采用温州地区人群 *HP* 耐药背景资料制定治疗方案,结果显示培养阳性组 *HP* 根除率为 90.2%,培养阴性组 *HP* 根除率为 87.4%,虽然前者高于后者,但差异无统计学意义,后者呋喃唑酮的药物毒副作用较大,因此,基于地区耐药背景指导下的 *HP* 根除治疗策略较盲目采用指南推荐方案取得的根除率高,应作为一种新的治疗思路,值得进一步推广和指导。 (北京协和医院消化内科 钱家鸣)

幽门螺杆菌高耐药地区基于人群耐药背景的幽门螺杆菌根除方案效果评价

潘杰 周晴接 吴建胜 林朗 施正超 刘云惠 刘秋香 杨宁敏 张建中

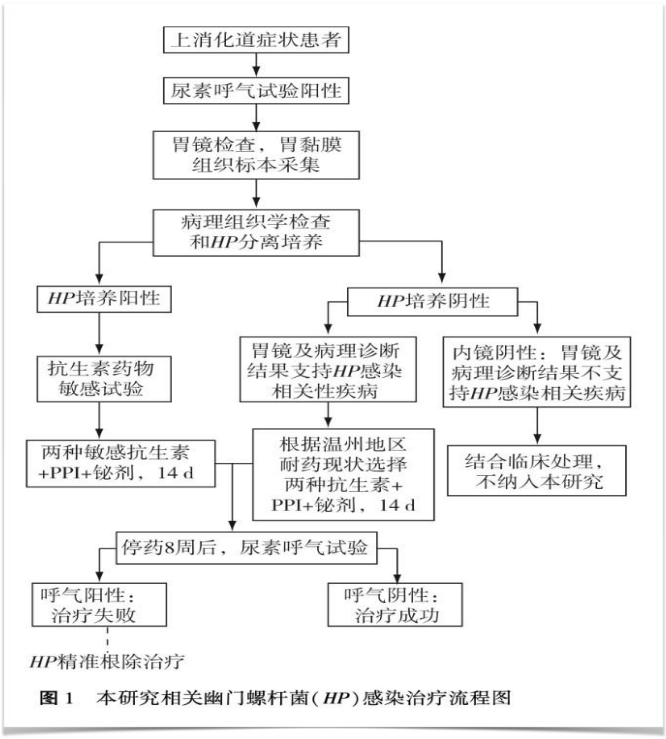


图 1　本研究相关幽门螺杆菌（*HP*）感染治疗流程图

日期：　　年　月　日

幽门螺杆菌感染根除治疗记录卡

姓名：		性别：		年龄：		联系电话：	
诊断：				□ 初治 / □ 复治		青霉素过敏：□是 □否	
诊断方式：	□ 尿素呼气试验 / □ 细菌培养 / □ 血清抗体						
药物	用法						
□ 艾司奥美拉唑	每次 20mg，一天 2 次（餐前半小时）						
□ 兰索拉唑	每次 30mg，一天 2 次（餐前半小时）						
□ 雷贝拉唑	每次 10mg 或 20mg，一天 2 次（餐前半小时）						
□ 奥美拉唑	每次 20mg，一天 2 次（餐前半小时）						
□ 胶体果胶铋	每次 200mg，一天 2 次（餐前半小时）						
□ 阿莫西林	每次 1000mg，一天 2 次（餐后）						
□ 呋喃唑酮	每次 100mg，一天 2 次或 3 次（餐后）（外购）						
□ 四环素	每次 500mg，一天 3 次或 4 次（餐后）（外购）						
□ 克拉霉素	每次 500mg，一天 2 次（餐后）						
□ 左氧氟沙星	每次 500mg，一天 1 次（餐后）						
□ 甲硝唑	每次 400mg，一天 3 次或 4 次（餐后）						

注意事项：

1. 严格按上述方案治疗，**疗程 14 天**，注意服药时间；
2. 停药后 4-8 周复查尿素呼气试验（**空腹检查**）；
3. 治疗过程中**禁烟酒、忌辛辣食物**；
4. 服药过程中可能出现大便颜色偏黑、口苦、腹胀不适、恶心、便秘、腹泻等情况，如症状较轻、短时间内自行消退的可继续服药，如较重或出现皮疹、发热等情况，需停药并及时医院就诊；
5. 复诊时请**携带此记录卡**；
6. 不良反应记录：_____
7. 其他备注：_____

治疗后复查时间：_____　呼气试验结果：_____

医生签字：_____

打开微信扫一扫下方二维码
关注“**胃肠健康公共平台**”

HP高耐药地区基于人群耐药背景的HP根除方案效果评价

上海大学附属第二医院 The Second Affiliated Hospital of Shanghai University 1897 温州市中心医院 Wenzhou Central Hospital

- 方法：对 271 例符合纳入标准的HP 感染患者进行前瞻性队列研究。
- 结果：HP 培养阳性组184 例，通过个体化治疗 HP 根除率为90. 2%(166/ 184)；HP 培养阴性组 87 例，依据耐药背景治疗HP 根除率为87. 4%，两者之间差异无统计学意义(χ^2=0.506，P=0.477)。
- 结论：基于地区耐药背景指导下的HP根除策略取得了较高的根除率，可以作为一种新的治疗方案应用于临床。

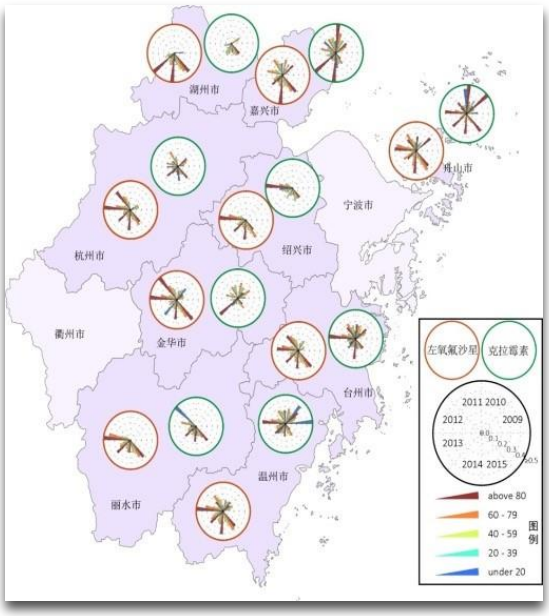
不同克拉霉素剂型治疗幽门螺杆菌感染的疗效分析

- 目的：探讨不同克拉霉素剂型治疗幽门螺杆菌感染的疗效 。
- 方法：回顾性分析2013年10月至2019年6月间就诊使用含克拉霉素铋剂四联方案进行幽门螺杆菌根除治疗的患者资料,比较两种不同克拉霉素制剂(速释片与缓释片)治疗幽门螺杆菌感染的根除率。
- 结果：共有316例符合条件的患者纳入本研究,其中,速释片组169例,缓释片组147例;速释片组的幽门螺杆菌根除率为90.53%(153/169),缓释片组的幽门螺杆菌根除率为 80.27%(118/147),速释片组明显高于缓释片组(P<0.05)。
- 结论：含克拉霉素铋剂四联方案根除治疗幽门螺杆菌感染的效果速释片优于缓释片 ,临床应用中建议优先选择克拉霉素速释片 。

.《浙江临床医学》 2020年第12期1802-1803

个体化治疗的概念?

- 基于HP细菌培养及药敏结果
- 基于HP基因型药敏检测结果?
- 基于本地区HP感染人群的耐药背景



项目一：^{13}C 尿素 45mg 片剂在成人Hp感染诊断中的准确性评价

研究背景

- 幽门螺杆菌（Helicobacterpylori，HP）感染已经被定义为一种感染性疾病，并与消化性溃疡、慢性胃炎、胃癌及胃黏膜相关淋巴组织样淋巴瘤（MALT）等疾病密切相关。目前我国 Hp 现症感染率约为 40% ~ 60% ，Hp 及其相关疾病负担沉重。根除 Hp 可起到“一石三鸟”的作用，即短期治疗(一石) 可预防胃癌、预防和治疗消化性溃疡、预防和治疗 Hp 相关消化不良(三鸟) ，具有很高的成本-效益优势[1]。预期在未来的 20 ~ 30 年中，检测和根除 Hp 仍将是消化系统疾病防控的热点。
- 准确诊断 Hp 感染是有效防控的前提，然而我国 Hp 感染检测的准确性仍存在不少问题。 UBT 是 Hp 非侵入性检测中最重要的方法，经考核建立的方法敏感性和特异性均接近 95% ，因此被视为 Hp 非侵入性检测的“金标准”。目前常用的^{13}C尿素剂型有散剂（粉剂）、胶囊和片剂；常用剂量为75mg、50mg和45mg，使用最多的是75mg制剂。本研究的目的是评价“^{13}C 尿素 45mg 片剂在成人Hp感染诊断中的准确性”。

项目一：^{13}C 尿素 45mg 片剂在成人Hp感染诊断中的准确性评价

流程：

目标人群签署知情同意书后，研究者需对受试者资料进行审核，并确认受试者符合入选标准且不符合排除标准。在入选10天内，先后完成 ^{13}C 尿素呼气试验和内镜检查。内镜检查分别于胃窦和胃体各取2块胃黏膜标本，分别进行组织病理学检测与尿素酶试验。对有不良事件的受试者需进行随访。

Hp 感染的诊断标准（金标准）：

1. 尿素酶试验结果判定：两个标本中只要有一个检测结果为阳性，即判定为阳性；两个标本检测结果均为阴性，判定为阴性。
2. 组织病理学结果判定：两个标本中只要有一个检测结果为阳性，即判定为阳性；两个标本检测结果均为阴性，判定为阴性。
3. 诊断标准：尿素酶试验及组织病理学结果判定均为阳性，即判定为Hp感染阳性。尿素酶试验及组织病理学结果均阴性，即判定为Hp阴性。如尿素酶试验与组织病理学结果判定相反，则予剔除。

评价内容：

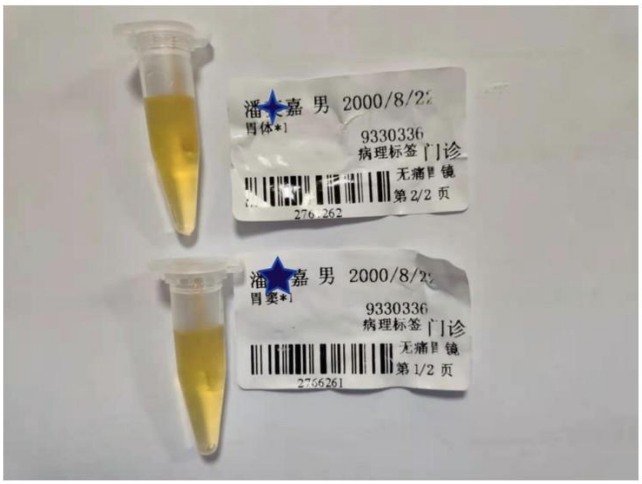
- **与 Hp 感染的诊断标准（金标准）相比较，^{3}C尿素45mg片剂诊断患者Hp 感染的敏感性、特异性、准确性、阳性预测值和阴性预测值。**

项目一：^{13}C 尿素 45mg 片剂在成人Hp感染诊断中的准确性评价

检测设备及试剂盒

(BreathID®Hp Lab System及海德润C13 尿素片剂)

项目一：^{13}C 尿素 45mg 片剂在成人Hp感染诊断中的准确性评价



序号	姓名	尿素呼气试验定量检测结果	尿素呼气试验定性检测结果	尿素酶检测结果		组织病理检测结果	
				胃窦	胃体	胃窦	胃体
1	WXY	0.5	阴性	阴性	阴性	阴性	阴性
2	HYZ	0.9	阴性	阴性	阴性	阴性	阴性
3	LSF	-0.9	阴性	阴性	阴性	阴性	阴性
4	WBL	60.1	阳性	阴性	阴性	阳性	阳性
5	ZXQ	0.3	阴性	阴性	阴性	阴性	阴性
6	SGH	7.8	阳性	阳性	阳性	阳性	阳性
7	CG	29.9	阳性	阳性	阳性	阳性	阴性
8	ZYL	22.5	阳性	阳性	阴性	阳性	阴性
9	HAF	1.3	阴性	阴性	阴性	阴性	阴性
10	KMM	39.5	阳性	阳性	阳性	阳性	阳性
11	ZQW	-0.1	阴性	阴性	阴性	阴性	阴性
12	TLF	-0.5	阴性	阴性	阴性	阴性	阴性
13	CXL	0.5	阴性	阴性	阴性	阴性	阴性
14	HGP	-0.4	阴性	阴性	阴性	阴性	阴性
15	XXY	-0.1	阴性	阴性	阴性	阴性	阴性
16	ZX	-0.6	阴性	阴性	阴性	阴性	阴性
17	WYH	1.3	阴性	阴性	阴性	阴性	阴性
18	SZX	18.7	阳性	阳性	阴性	阳性	阳性
19	YYY	60.6	阳性	阳性	阳性	阳性	阳性
20	WJX	44.4	阳性	阳性	阳性	阳性	阳性
21	DYY	-0.5	阴性	阴性	阴性	阴性	阴性
22	ZLC	0	阴性	阴性	阴性	阴性	阴性
23	FY	-0.9	阴性	阴性	阴性	阴性	阴性
24	SXY	20.8	阳性	阳性	阴性	阴性	阴性
25	WBL	0.9	阴性	阴性	阴性	阴性	阴性
26	JJB	2.3	阴性	阴性	阴性	阴性	阴性

序号	姓名	尿素呼气试验定量检测结果	尿素呼气试验定性检测结果	尿素酶检测结果		组织病理检测结果	
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2	HYZ	0.9	阴性	阴性	阴性	阴性	阴性
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5	ZXQ	0.3	阴性	阴性	阴性	阴性	阴性
6	SGH	7.8	阳性	阳性	阳性	阳性	阳性
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21	DYY	-0.5	阴性	阴性	阴性	阴性	阴性
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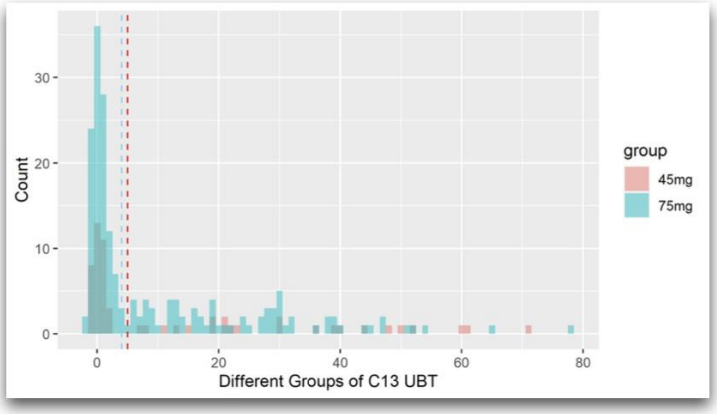
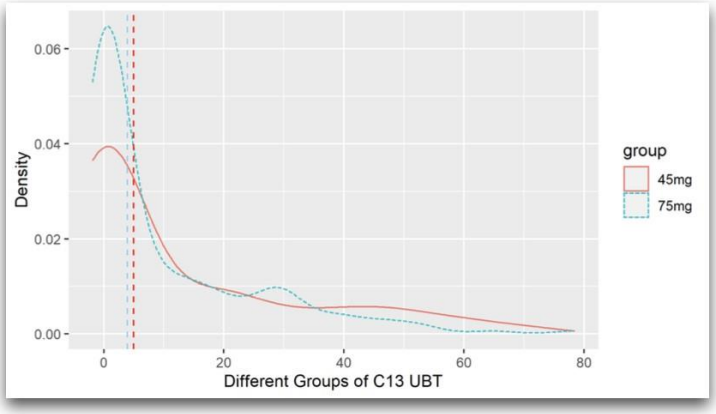
24	SXY	20.8	阳性	阳性	阴性	阴性	阴性
25	WBL	0.9	阴性	阴性	阴性	阴性	阴性
26	JJB	2.3	阴性	阴性	阴性	阴性	阴性

项目一：^{13}C 尿素 45mg 片剂在成人Hp感染诊断中的准确性评价





^{13}C 尿素 45mg 片剂和 75mg 胶囊检测的DOB值距离cutoff值平均差方分别是435，256

幽门螺杆菌诊断进展

兰春慧　教授 主任医师

陆军军医大学大坪医院消化科副主任

博士生导师

我国恶性肿瘤的发病率及死亡率

Table 1 Age-standardized cancer incidence and mortality rates per 100,000 populations by gender in China in 2018

Index	Gender	All cancers	Rank									
			1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
Incidence	Both	201.7	Breast	Lung	Colorectum	Stomach	Liver	Esophagus	Cervix uteri	Thyroid	Prostate	Corpus uteri
			36.1	35.1	23.7	20.7	18.3	13.9	10.7	10.1	9.1	7.1
	Male	223.0	Lung	Stomach	Colorectum	Liver	Esophagus	Prostate	Pancreas	Bladder	Leukemia	NHL
			47.8	29.5	28.1	27.6	19.7	9.1	6.2	5.9	5.8	4.8
	Female	182.6	Breast	Lung	Colorectum	Thyroid	Stomach	Cervix uteri	Liver	Esophagus	Corpus uteri	Ovary
			36.1	22.8	19.4	15.8	12.3	10.7	9.0	8.2	7.1	5.3
Mortality	Both	130.1	Lung	Stomach	Liver	Esophagus	Colorectum	Breast	Pancreas	Prostate	Cervix uteri	Leukemia
			30.9	17.5	17.1	12.7	10.9	8.8	4.9	4.7	4.4	3.5
	Male	166.6	Lung	Liver	Stomach	Esophagus	Colorectum	Pancreas	Prostate	Leukemia	Brain, CNS	NHL
			43.4	25.6	25.0	18.2	13.1	5.6	4.7	4.4	3.6	2.8
	Female	95.2	Lung	Stomach	Colorectum	Breast	Liver	Esophagus	Cervix uteri	Pancreas	Ovary	Brain, CNS
			19.0	10.4	8.8	8.8	8.6	7.4	4.4	4.2	2.9	2.8

CNS, central nervous system; NHL, non-Hodgkin lymphoma. The estimates are from Global Cancer Observatory 2018, IARC, 2018 (6). Age-standardized rates are calculated using the direct method and the world standard population.

我国属于胃癌高发国家：胃癌发病率居我国恶性肿瘤第2位，死亡率居第2位

Sun D, Cao M, Li H et al Chin J Cancer Res. 2020;32(2):129-139.

胃癌发生的危险因素

正常胃黏膜 → 慢性浅表性胃炎 → 慢性萎缩性胃炎 → 肠上皮化生 → 异型增生 → 胃癌

- 高盐饮食、腌熏煎烤炸食品、不良饮食习惯
- 吸烟饮酒
- Hp 感染
- 遗传因素
- .....

胃癌的发生是多因素参与、多步骤演变的复杂病理过程，

Hp感染的流行病学

Table 1. The prevalence of *Helicobacter pylori* infection and associated risk factors

Region/country	No. of subjects	*Helicobacter pylori* infection		Ref.
		Prevalence (%)	Risk factor	
USA	7465	32.5	Age (>70 years old) Ethnicity (African American)	34
USA	7495	25.4%	Non-US born Soil-related occupation Crowded living condition Water supply from well	35
Latin Americas	1852	79.4	Increased no. of siblings Low education level Low household conditions Crowding	37
Turkey	4622	82.4	Geographical region Male gender Low education level Older age Low socioeconomic status	38
Latvia	101	15.6	Diet (less consumption of fruits)	39
Portugal	2067	84.2	Low education level Age (>70 years old) Living in deprived neighbourhood	40
Japan	21 144	27.5	Older age (>60 years age)	42
Korea	10 796	54.4	Male gender Older age Low income Residence in rural area Higher cholesterol level Low education level	43
China	2006	83.4	Urban and suburban (infection with type 1 *H. pylori* strains) Manual type of occupation	44

USA, the United State of America.

在世界范围内，Hp感染在亚洲、中美洲和南美国家中最高

与年龄、种族等因素明显相关，

我国Hp感染率可达57.6%

Sukri, A, Hanafiah, A, et al. APMIS 2020; 128: 150 – 161.

早期胃癌筛查

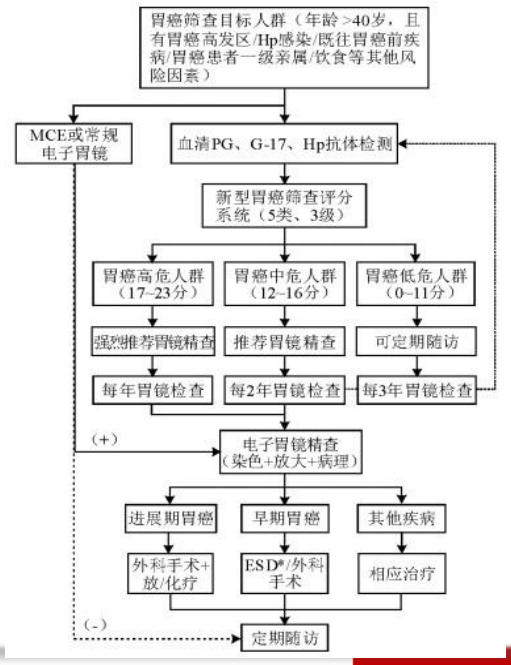


表1　新型胃癌筛查评分系统

变量名称	分类	分值
年龄(岁)	40~49	0
	50~59	5
	60~69	6
	>69	10
性别	女	0
	男	4
Hp感染	无	0
	有	1
PGR	≥3.89	0
	<3.89	3
G-17(pmol/L)	<1.50	0
	1.50~5.70	3
	>5.70	5

杜奕奇,蔡全才,等.[J].胃肠病学,2018,23(02):92 -97.

Hp感染与多种疾病有关

胃部疾病

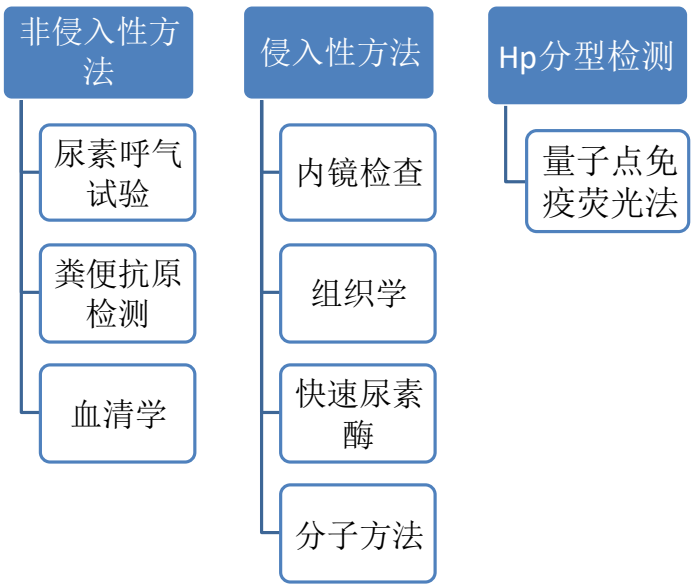
- 胃炎
- 消化性溃疡
- 胃癌
- MALT 淋巴瘤
- ……

胃外疾病

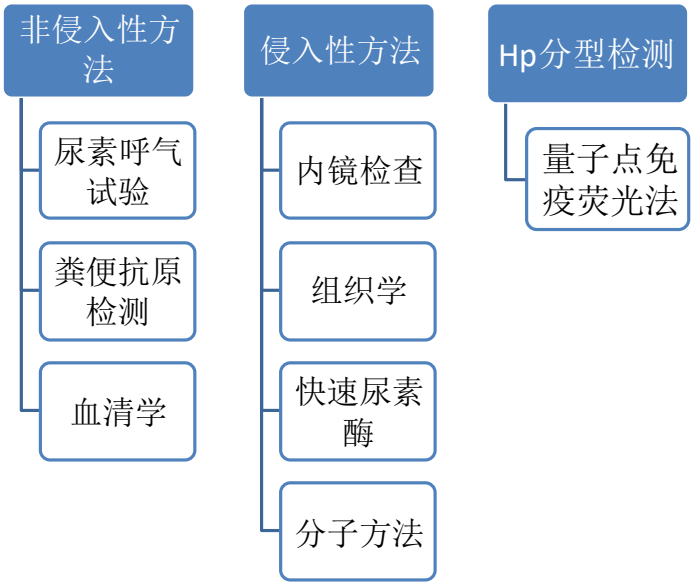
- 特发性血小板减少性紫癜　；
- 缺铁性贫血 ；
- 偏头痛，冠心病，脑梗死；
- 糖尿病伴胃轻瘫 ；
- 妊娠剧吐，胎儿生长受限 ；
- 荨麻疹，酒糟鼻；
- 不孕不育
- ……

研究证实一旦感染H．pylori，不经治疗难以自愈，10％～15％的H.pylori感染者发展为消化性溃疡，约5％发生胃黏膜萎缩，<1％的感染者发展为胃癌或MALT淋巴瘤。

Hp感染诊断



Hp感染诊断



粪便抗原检测（ SAT）

☑ **酶联免疫吸附试验（ ELISA ）**

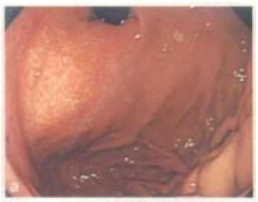
- 灵敏度、特异度、准确度较高
- 操作相对麻烦，耗时长
- 胃上皮细胞每 1~3 天更新 1 次，在其更新的过程中，脱落的上皮细胞及在其表面定植的 Hp 脱落后随粪便排出体外，由于检测的是随粪便排出的 Hp 抗原，因此可反映 Hp 的现症感染情况

王纯明，贾东明，张宝伟 .[J]. 检验医学与临床， 2015 ， 12 （23）： 139 -141.

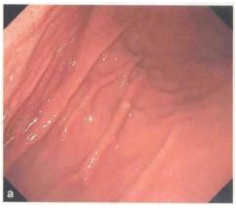
Hp血清学检测

- **Hp 血清学检测方法主要包括 ELISA 和Hp 快速检测试剂盒法等**
  - 检测结果不受近期用药和胃内局部病变影响
  - 由于 Hp 感染后血清中抗体出现需要半年左右的时间，故早期查抗体易出现假阴性。 Hp 被根除后，抗体水平下降缓慢，一般 1~2 年才能转阴，在此期间检测结果阳性则表示患者可能曾经感染过 Hp 或正在感染期间，不能区分感染的具体情况。因此， Hp 血清学检测有一定局限性，不宜用于评价 Hp 根除效果，多用于 Hp 感染的流行病学调查

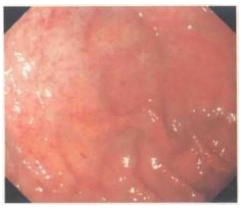
内镜检查



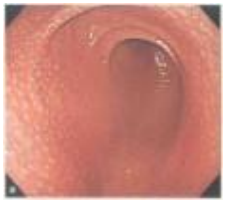
萎缩



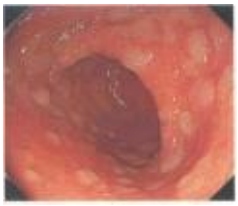
弥漫性发红



点状发红



鸡皮样



肠上皮化生

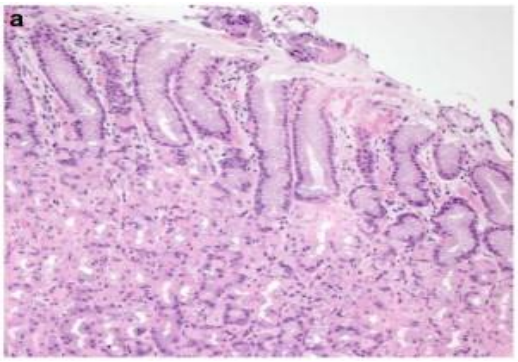
Hp 感染可以通过内镜下的特征来初步诊断，《京都胃炎分类》显示，普通白光内镜下 Hp 感染的黏膜特征性表现包括：萎缩、点状发红、弥漫性发红、脊状发红、地图状发红、黏膜肿胀、肠上皮化生、凹陷性糜烂、增生性息肉、胃底腺息肉、黄色瘤、鸡皮样改变、多发性白色扁平隆起等表现。

诊断准确率欠高，需要专门设备，检查费时长

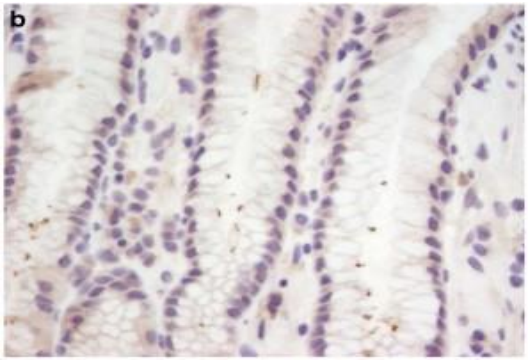
加藤元嗣，井上和彦，村上和成，等.[M].沈 阳：辽宁科学技术出版社，2018： 27-31.

组织学检查

- 组织学是诊断 Hp 感染最准确的方法
- 但当慢性活动性胃炎通过 HE 染色法未检测到 Hp 感染或存在罕见、特殊细菌感染的情况时，需补充免疫组织化学



轻度至无炎症，HE染色未见HP



免疫组化检测后可见HP

快速尿素酶测试（RUT）

- **在临床医学中， RUT 是最为常见的 Hp 感染检测方法**
  - 该检测方法能够直观有效地检查出患者是否感染 Hp，具有快速、操作方便的优点，适用于首次进行胃镜检查的患者
  - 患者接受检测前口服抗生素、使用质子泵抑制剂（ PPI ）、铋剂等药物，这些药物可使尿素酶活性受到抑制，从而影响检测结果
  - 因其在胃镜下进行，患者有一定的痛苦， 且不适用于合并严重心、脑、肺疾病患者
  - 检测结果易受取材部位、环境温度、试剂 PH 值、组织大小、细菌量、观察时间等因素影响

分子方法

- 现代分子检测主要基于实时聚合酶链式反应 （polymerase chain reaction ，PCR ）技术，此项技术不但可以检测 Hp，并且对 Hp 抗生素耐药性同样适用 （Hays 等的研究报道显示， PCR 技术在检测 Hp 感染中的敏感性可达 88.5%）
- 微滴式数字 PCR （droplet digital PCR ，ddPCR ）系统是在传统的 PCR 扩增前对样品进行微滴化处理， 将含有核酸分子的反应体系分成成千上万个纳升级的微滴，经 PCR 扩增后逐个对每个微滴进行检测 （Talarico 等运用 ddPCR 检测了经组织学诊断为 Hp 感染的患者，其 Hp 感染的检出率可达 93%）
- Hp 根除治疗失败时，扩增受阻突变体系 PCR 可用于检测耐药（如克拉霉素）

细菌培养

- 可用于诊断、药敏检测、细菌学研究
- 有一定的技术要求，敏感性低，特异性高，一般不推荐单纯用于幽门螺杆菌的诊断

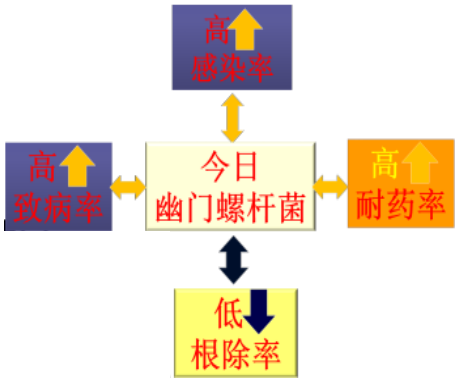
Hp目前诊疗现状——根除指征存在争议

大规模根除Hp可能带来的问题

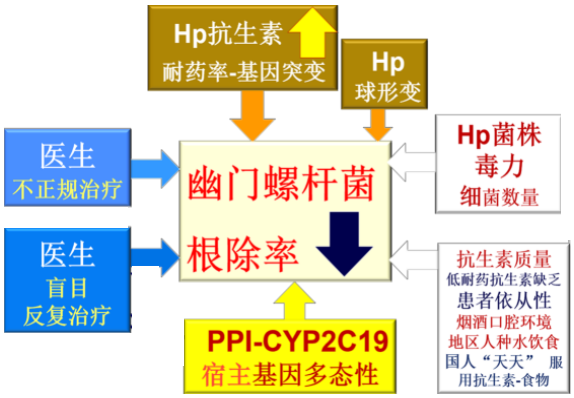
- **医疗负担重** ⋯→ 8000亿！
- **肠道菌群失调** ⋯→ 腹泻、二重感染等
- **过敏性疾病发生** ⋯→ 过敏性哮喘、皮炎等
- **反复根除失败及耐药** ⋯→ 无药可用！

Hp目前诊疗现状

Hp感染诊治现状



Hp根除率下降的原因



治还是不治？

面临问题：

1、大部分Hp感染者不表现症状，阳性结果的体检者到底应不应该用药？不用药→增加了患者的心理压力

2、如果对Hp“格杀勿论”，面临的抗生素耐药等问题该如何解决？用药→身体承受各种副作用

3、能否只针对强毒菌株进行根除治疗，实现精准治疗？

Hp的精准诊断与治疗

毒力分型是今后对Hp精准治疗的方向

2019年共识

·标准与规范·

中国幽门螺杆菌根除与胃癌防控的专家共识意见(2019年,上海)

国家消化系统疾病临床医学研究中心(上海) 国家消化道早癌防治中心联盟 中华医学会消化病学分会幽门螺杆菌学组 中华医学会外科学分会胃癌学组 中华医学会健康管理学分会 中国医师协会内镜医师分会消化内镜专业委员会 中国医师协会内镜医师分会消化内镜健康管理与体检专业委员会 中国抗癌协会肿瘤内镜专业委员会
通信作者:李兆申,海军军医大学附属长海医院消化内科,上海 200433,Email:zhsl@vip.163.com,电话:021-55621735;陈旻湖,中山大学附属第一医院消化科,广州 510080,Email:chenminhu@vip.163.com,电话:020-87755766;吕农华,南昌大学第一附属医院消化科 330006,Email:lunonghua@163.com,电话:0791-88691290;周丽维,北京大学第三医院消化科 100191,Email:zhoumed@126.com,电话:010-62034716

【陈述 17】Hp 的细胞毒素相关基因 A(cytotoxin associated gene A,CagA)和空泡变性细胞毒素 A(vacuolation toxin A,VacA)血清抗体检测,亦可用于 Hp 筛查,对 Hp 毒力阳性的菌株更推荐根除。(证据质量:低,共识水平:80.0%)

2019年共识

中华健康管理学杂志 2019 年 8 月第 13 卷第 4 期 Chin J Health Manage, August 2019, Vol. 13, No. 4 · 285 ·

·标准与规范·

中国幽门螺杆菌根除与胃癌防控的专家共识意见(2019年,上海)

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通信作者:李兆申,海军军医大学附属长海医院消化内科,上海 200433,Email:zhsl@vip.163.com,电话:021-55621735;陈旻湖,中山大学附属第一医院消化科,广州 510080,Email:chenminhu@vip.163.com,电话:020-87755766;吕农华,南昌大学第一附属医院消化科 330006,Email:lunonghua@163.com,电话:0791-88691290;周丽雅,北京大学第三医院消化科 100191,Email:zhoumed@126.com,电话:010-62034716

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Hp的关键毒力因子

H.pylori 菌株的基因型多态性与其致病性有密切的关系，多种毒力因子已被发现，如：细胞毒素相关蛋白A（CagA）、空泡细胞毒素A（VacA） 尿素酶（Ure ）、 血型抗原结合黏附素（BabA）、 前炎症外膜蛋白（OipA） 、十二指肠溃疡诱导因子（DupA）、中性粒细胞激活蛋白 （NAP）、黏附相关蛋白A （alpA）、 脂多糖（LPS ） 、热休克蛋白60（Hsp60 ）等，新的毒力因子仍不断被发现。 其中最主要的是VacA和CagA。

Hp的分型

Ⅰ型：毒力强
CagA（+）
VacA（+）
Ure （+）

Ⅱ型：毒力弱
CagA（-）
VacA（-）
Ure （+）

Ⅰ型：Hp 菌株能产生空泡毒素（VacA）和细胞毒素相关蛋白（CagA），致使出现广泛的组织炎症，易引发胃炎及溃疡病。

Ⅱ型：Hp即CagA 和VacA 阴性株不产生毒力因子VacA 和CagA，此类HP 菌株毒性较小，感染后不表现症状或只引起轻度的慢性浅表性胃炎。

精准诊疗

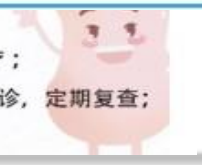
项 目	结 果						说 明
Ure	—	+		+			尿素酶：判断HP是否存在的依据
CagA	—	—		+	—	+	细胞毒素：释放炎症因子，引起炎症发生
VacA	—	—		—	+	+	空泡毒素：诱导细胞发生空泡变性
判断	无感染	有感染 II型弱毒性		有感染 I型强毒性			HP根除治疗推荐使用四联方案，请在医生指导下进行。
症状	无	无	有	有/无			
建议	/	随诊	对症治疗	建议根除治疗			

结果建议：

I型强毒株：VacA/CagA单阳性或全阳性；易引发胃炎、胃溃疡，建议进行根除性治疗；

II型弱毒株：VacA/CagA全阴性，Ure阳性；无症状或轻度的慢性浅表性胃炎，建议随诊，定期复查；

无感染：VacA/CagA/Ure全阴性；未感染幽门螺杆菌（HP）。

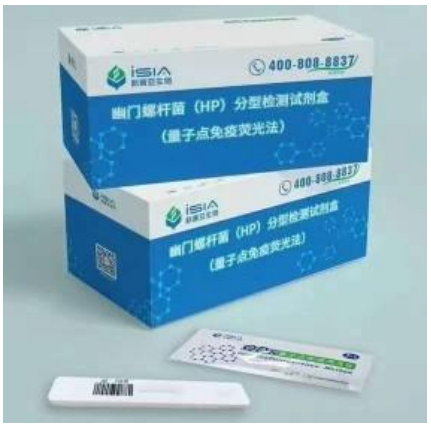


量子点免疫荧光法优势

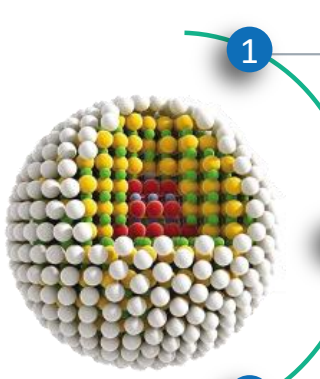
无须空腹，早晚可查。

无需服药，滴血可查。

老幼孕宜，人人可查。



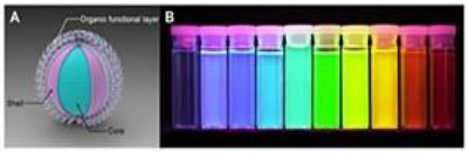
量子点免疫荧光法

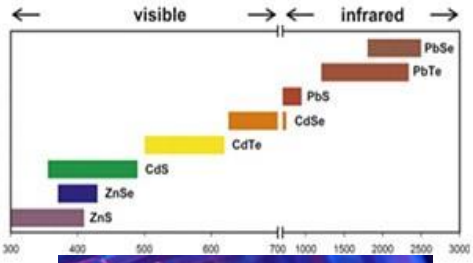


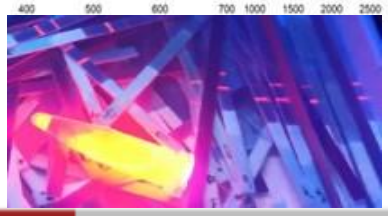
1 纳米晶体

2 半导体

3 2-10纳米直径





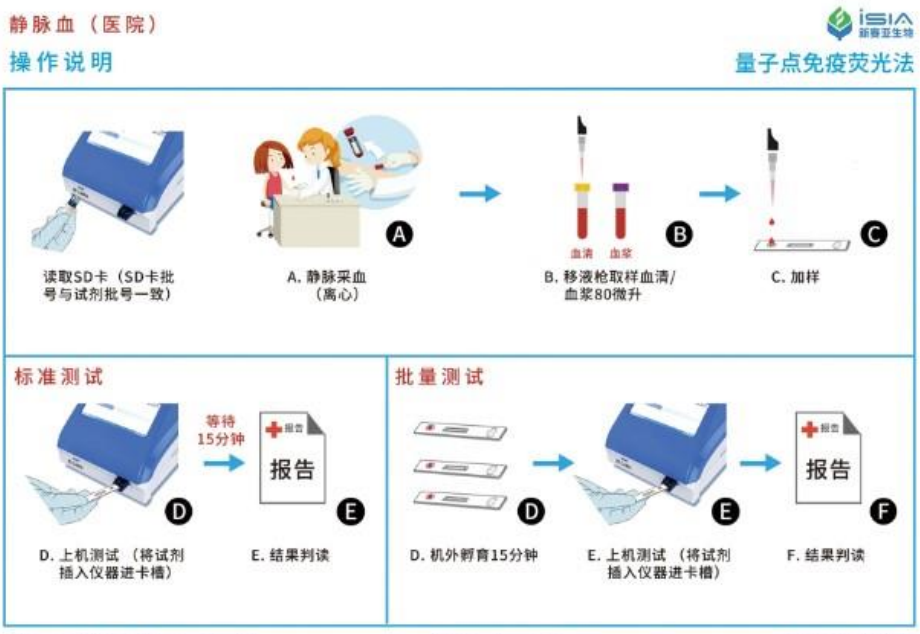


量子点技术被《science》评为年度十大科学突破技术。

量子点免疫荧光法

信号物质	胶体金	有机荧光	化学发光	量子点发光
基本原理	显色物质	有机物发光	化学反应发光	**物理材料发光**
信号灵敏度	低	一般	高	**高**
信号检测范围	窄	一般	宽	**宽**
产品定性/定量	定性/半定量	定量	定量	**定量**
稳定性	不稳定	不稳定	衰减快	**非常稳定**
对检测设备要求	一般	一般	要求高	**一般**
单人份材料成本	低	高	较高	**低**

量子点免疫荧光法优势



量子点免疫荧光法优势

只需 80 微升血清 ，即可快速检测出 Hp 的多项毒素，将Hp 菌株分为 Ⅰ型(强毒株)和Ⅱ型(弱毒株)

检测不受食物药物影响，无特殊人群限制

操作简单，滴加血清到检测卡，插入仪器，15分钟出结果，

仪器判断，可出数值

常温保存，单人份包装

单通道、多通道、全自动仪器自由选择，适用不同的场景

医保范围，经济实惠，适合大规模筛查

Hp诊治展望

个体化治疗

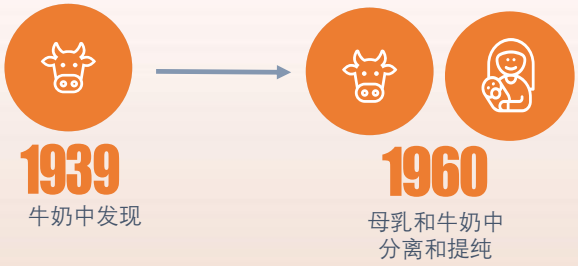
- 确定最合适的治疗时机
- 选择最合适的治疗方式
- 达到最佳的治疗效果

  最小的药物副反应

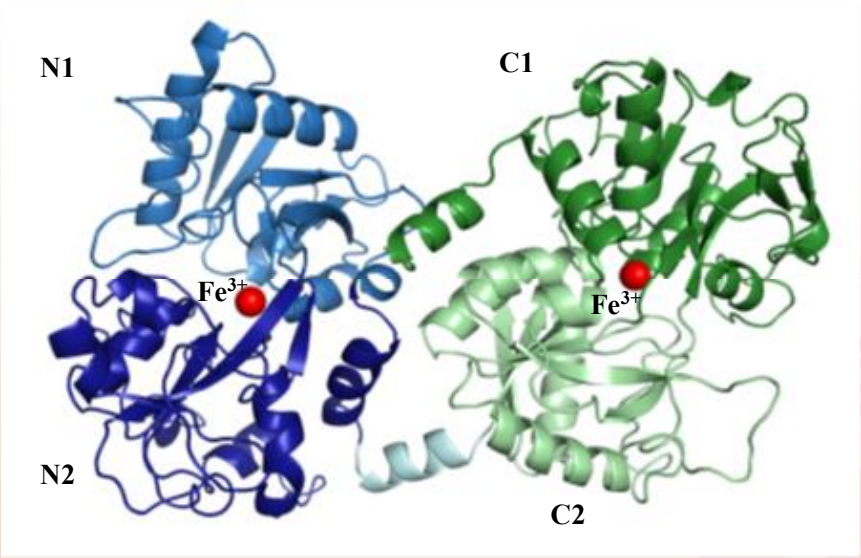
  最少的耐药性

乳铁蛋白研究进展

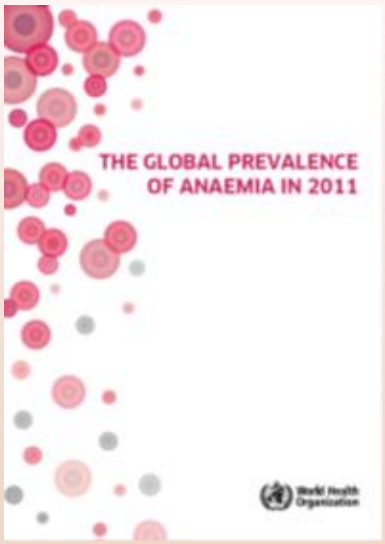
北京大学第一医院 消化内科 董锦沛



乳铁蛋白的结构

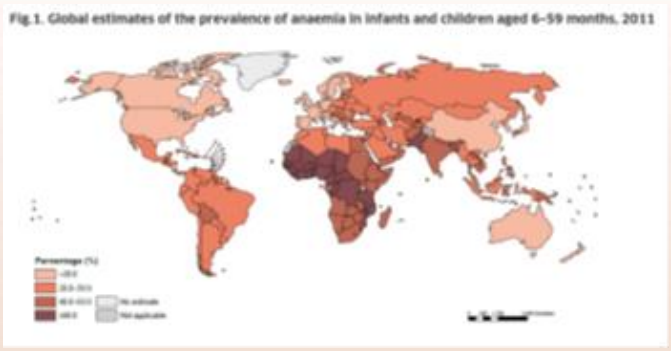


乳铁蛋白的蛋白质结构由两个球形叶（N-叶和C-叶）组成，由α-螺旋连接。



World Health Organization

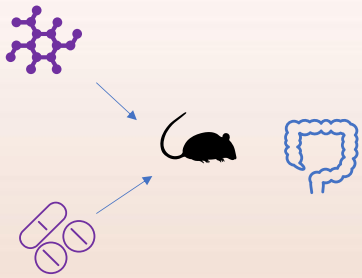
WHO: THE GLOBAL PREVALENCE OF ANAEMIA IN 2011



WHO: THE GLOBAL PREVALENCE OF ANAEMIA IN 2011

乳铁蛋白在缺铁性贫血中的应用

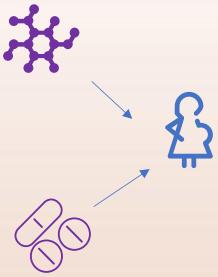
乳铁蛋白



硫酸亚铁

1988年 Kawakami

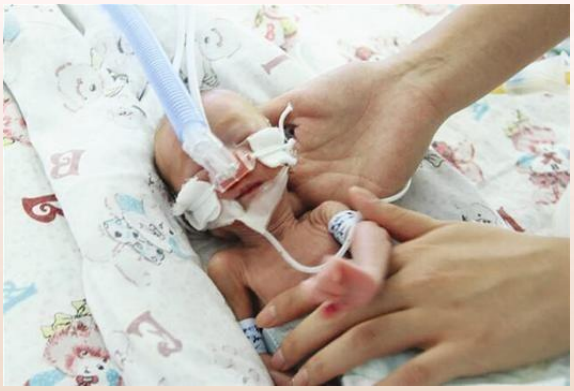
乳铁蛋白



硫酸亚铁

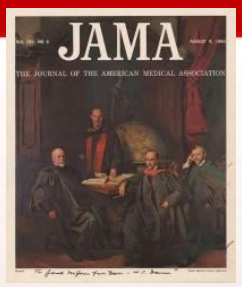
Paesano et al., 2010

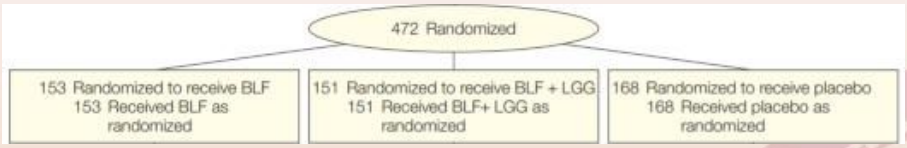
乳铁蛋白



Randomized Controlled Trial 56.272 1区 > JAMA. 2009 Oct 7;302(13):1421-8.
doi: 10.1001/jama.2009.1403.

Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial





9/153 [5.9%]	7/151 [4.6%]	29/168 [17.3%]

Risk ratio, 0.34， P=0.002 for BLF vs control
Risk ratio, 0.27， P=0.001 for BLF plus LGG vs control

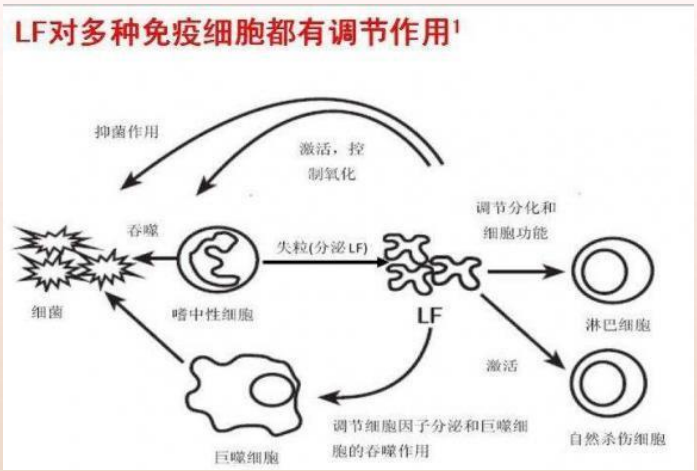
JAMA **2009** *302*, 1421–1428

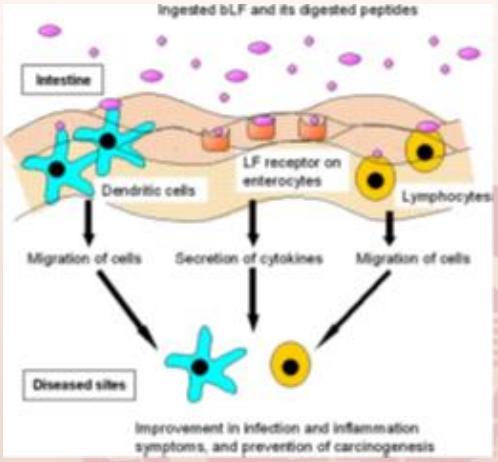
乳铁蛋白在新生儿坏死性小肠炎中的应用

婴儿	研究类型	干预措施	主要结果
极低体重新生儿（体重＜1500g）	多中心、随机、双盲、安慰剂对照RCT	bLf 或 bLf＋LGG 或安慰剂	bLf或bLf＋LGG组患儿坏死性小肠炎或死亡率明显下降，无不良反应发生[1]
极低体重新生儿（体重＜1500g）或小于32周	单中心、随机、双盲、安慰剂对照RCT	bLf 或安慰剂	bLf能够降低院内脓毒症风险，提高Treg细胞数目[2]
极低体重新生儿（体重＜2000g）	随机、双盲、安慰剂对照RCT	bLf 或安慰剂	bLf可以降低迟发脓毒症的发生率[3]
新生儿（体重＜2500g）	随机、双盲、安慰剂对照RCT	bLf 或安慰剂	bLf可以降低院内脓毒症次数，尤其在极低体重新生儿中[4]
极低体重新生儿（体重＜1500g）或小于32周	随机、双盲、安慰剂对照RCT	bLf 或 bLf＋LGG 或安慰剂	bLf能都降低严重坏死性小肠炎的发生率[5]
极低体重早产新生儿	多中心、随机、双盲、安慰剂对照RCT	bLf 或 bLf＋LGG 或安慰剂	bLf可以降低迟发脓毒症和坏死性小肠炎的发生率[6]

1. *Early Hum. Dev.* **2014**, *90* (Suppl. 1), S60–S65
2. *Am. J. Perinatol* **2014**, *31*, 1111–1120 3 . *J. Trop. Pediatr* **2015**, *61*, 370–376
4. *Pediat Infect. Dis. J.* **2015**, *34*, 571–576 5. *Neonatal Perinatal Med* **2017**, *10*, 249–255
6. *J. Pediatr.* **2018**, *193*, 62–67.e1

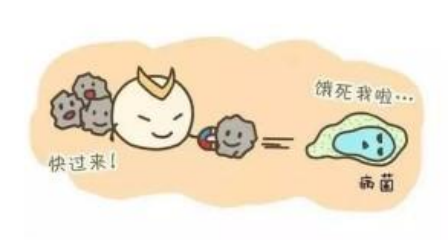
乳铁蛋白的免疫调节功能





乳铁蛋白对细菌的抗菌作用

LF对革兰阳性菌和革兰阴性菌均表现出了较强的抑菌作用。



LF 通过对铁的螯合作用

多数微生物都需要铁才能生长
LF 与铁的结合能力是转铁蛋白的300倍

破坏细菌细胞膜通透性

LF N-末端带正电荷的肽片段可与革兰氏阴性菌外膜带负电荷的LPS 产生静电相互作用，导致细菌外膜的结构紊乱

阻止细菌与宿主细胞的结合

LF 的N 端具有丝氨酸蛋白酶功能，能够降解入侵细胞所需要的毒力蛋白

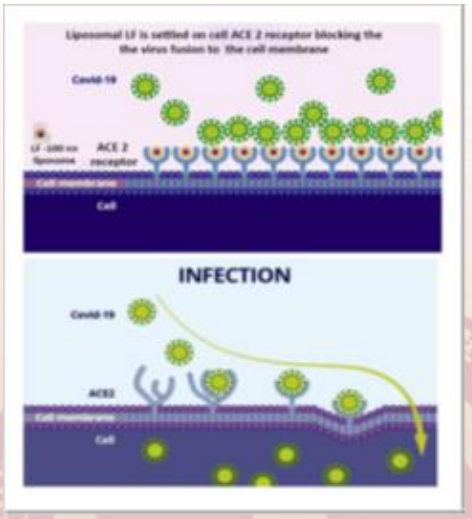
防止细菌粘附到目标细胞

竞争性结合目标细胞表面的膜糖胺聚糖来降低细菌的结合能力

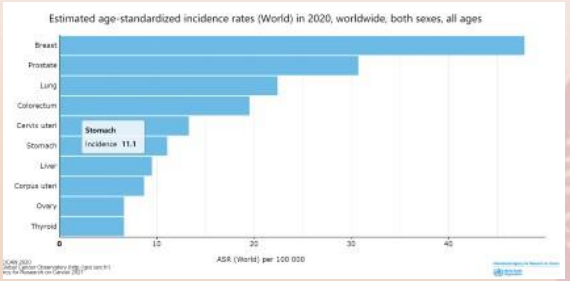
乳铁蛋白的抗病毒作用

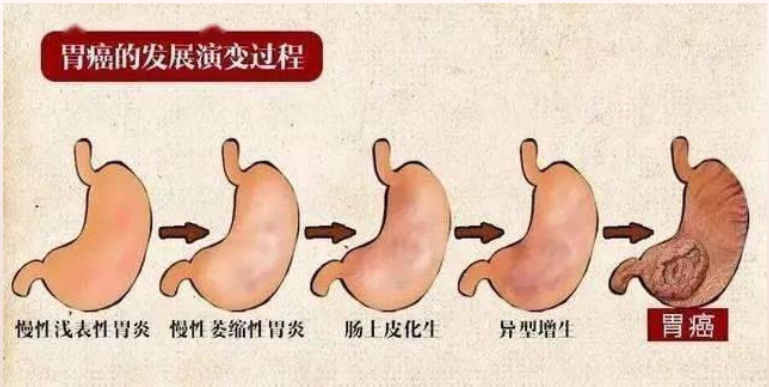
Liposomal Lactoferrin as Potential Preventative and Cure for COVID-19

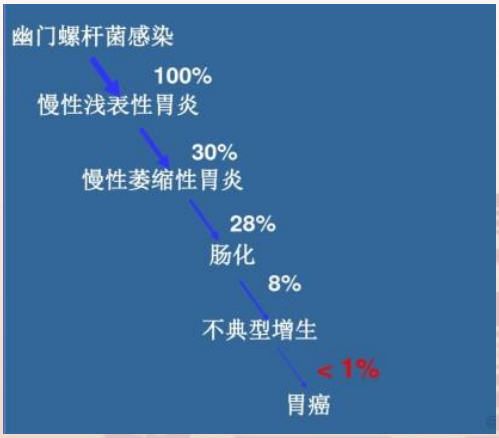
Gabriel Serrano[1,*], Iulia Kochergina[1], Arturo Albors[2], Eva Diaz[2], Mar Oroval[3], Guillen Hueso[1], Juan M Serrano[1]



胃癌的流行病学


Estimated age-standardized incidence rates (World) in 2020, worldwide, both sexes, all ages
Breast
Prostate
Lung
Colorectum
Cervix uteri
Stomach
Liver
Corpus uteri
Ovary
Thyroid
Stomach
Incidence 11.1
0
10
20
30
40
ASR (World) per 100 000


胃癌的发展演变过程
慢性浅表性胃炎
慢性萎缩性胃炎
肠上皮化生
异型增生
胃癌


幽门螺杆菌感染
100%
慢性浅表性胃炎
30%
慢性萎缩性胃炎
28%
肠化
8%
不典型增生
< 1%
胃癌

乳铁蛋白在根除幽门螺杆菌中的应用

Bovine lactoferrin enhances the efficacy of levofloxacin-based triple therapy as first-line treatment of *Helicobacter pylori* infection: an *in vitro* and *in vivo* study

Antonio Francesco Ciccaglione[1]†, Mara Di Giulio[2]†, Silvia Di Lodovico[2], Emanuela Di Campli[2], Luigina Cellini[2]* and Leonardo Marzio[1]

Alimentary Pharmacology & Therapeutics

Bovine lactoferrin for *Helicobacter pylori* eradication: an open, randomized, multicentre study

乳铁蛋白在根除幽门螺杆菌中的应用

Alimentary Tract

Use of bovine lactoferrin for *Helicobacter pylori* eradication

F. Di Mario[a,*], G. Aragona[a], N. Dal Bò[b], G.M. Cavestro[a], L. Cavallaro[a], V. Iori[a], G. Comparato[a], G. Leandro[c], A. Pilotto[d], A. Franzè[e]

Use of Lactoferrin for *Helicobacter pylori* Eradication

Preliminary Results

Francesco Di Mario, M.D., Giovanni Aragona, M.D., Nadia Dal Bò, M.D., Anna Ingegnoli, M.D., Giulia M. Cavestro, M.D., Ali M. Moussa, M.D., Veronica Iori, M.D., Gioacchino Leandro, M.D., Alberto Pilotto, M.D., and Angelo Franzè, M.D.

甘海胃康对昆明小鼠幽门螺杆菌标准菌株SS1感染治疗作用的实验研究及其对乙醇/阿司匹林/吲哚美辛所致胃黏膜损伤作用的研究

2021年12月11日

• 项目负责人： 杨桂彬 教授

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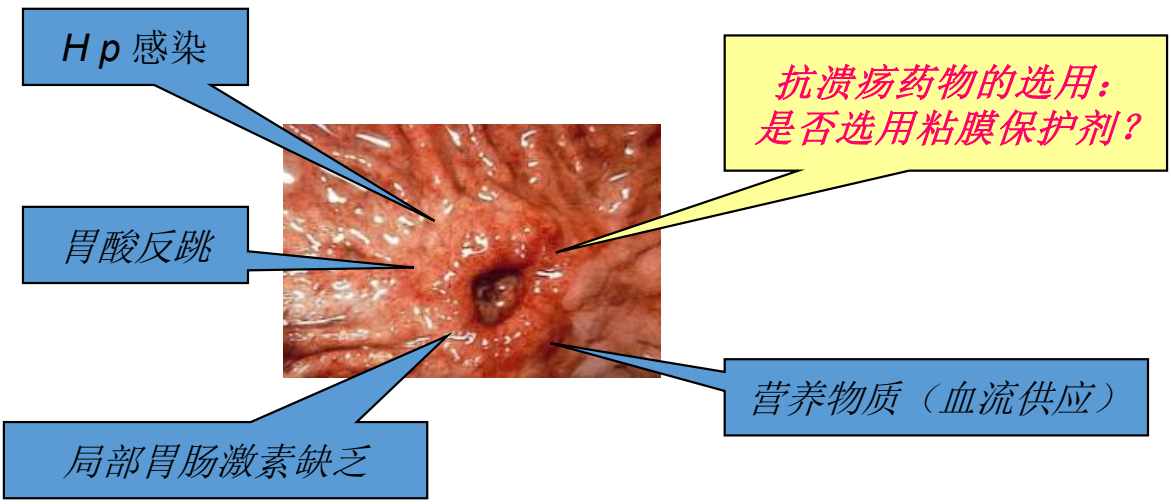
立题背景



主要的胃黏膜保护剂

- **单纯胃粘膜保护剂**
  - 硫糖铝
  - 前列腺素(喜克溃)
  - 替普瑞酮(施维舒)
  - 合欢青叶酯(吉法酯, 惠加强)
  - 双八面体蒙脱石(思密达)
  - 麦滋林-S颗粒
  - 马来酸依索拉啶(盖世龙)
  - 醋氨己酸锌(依安欣)
- **兼有杀灭Hp作用**
  - 丽珠得乐(枸橼酸铋钾)
  - 德诺(胶体次枸橼酸铋)
  - 胶态果胶铋(碱式果胶酸铋钾)
  - RBC
- **兼有抗酸作用**
  - 氢氧化铝
- **兼有抗酸抗胆汁作用**
  - 铝碳酸镁
- 中药黏膜保护剂
- ……

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中药的胃粘膜保护作用

- 中医所说的胃病，病理学基础就是胃黏膜的急、慢性炎症，是**胃粘膜屏障**的破坏，是胃黏膜损害因素和防御因素之间失衡的结果。
- 中药治疗胃病有自己的理论体系，但是从现代医学的角度诠释，必然是从缓解症状、修复黏膜两个角度起作用，因此，大部分治疗胃病的中药具有黏膜保护作用。

- 甘海胃康
- 三九胃泰
- 温胃舒、养胃舒
- 银杏叶
- 荆花胃康
- …. …. ….

立题背景

甘海胃康胶囊由八味传统中药材组成，能够通过改善胃肠功能、消化腺体功能以及修复胃肠粘膜的防御能力等方式，弥补一般西药以制酸治胃病的局限性，临床上和西药联用可有效治疗胃炎、胃食管返流征、消化性溃疡等多种常见胃部疾病。

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健脾和胃　　收敛止痛

白术：
主要成分苍术酮能够双向调节胃肠系统

甘草：
富含甘草苷、甘草酸、甘草菇醇等，有肾上腺皮质激素作用，能够抗炎、抗溃疡

海螵蛸：
乌贼内壳，含碳酸钙85%以上，制酸效果显著

绞股蓝：
富含140余种皂苷，能增加胃黏膜细胞新陈代谢，促进肉芽组织生长和溃疡闭合

黄 柏：
含有小檗碱，有广谱抗菌作用可抑杀HP

枳 实：
富含挥发油类，能使胃肠运动收缩节律增加

沙 棘：
富含大量维生素、氨基酸，有抗自由基作用

延胡索：
延胡索乙素对胃肠道疼痛有强烈镇痛效果；
去氢延胡索甲素能有效抗溃疡

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沙棘、绞股蓝总苷 ➡ 修复胃粘膜

沙棘：富含八大类160余种天然活性成分抗炎生肌、促进组织再生的作用；清除人体自由基的作用。
绞股蓝总苷：抗溃疡，增加胃溃疡边缘组织的黏膜血流量和氧含量，有利于组织修复，从而使溃疡面积缩小，达到治疗效果

黄柏、甘草、延胡索 ➡ 抑杀HP

抗炎、抑杀HP、抗溃疡等作用。相互配伍其抑菌作用多可产生协同或相加作用

白术、枳实、甘草 ➡ 促进胃肠动力、消化吸收

枳实、白术水煎液具有调节免疫力、兴奋胃肠道平滑肌的功效，二药配伍对试验动物胃排空、肠推进及胃泌素、胃动素的分泌有促进作用

海螵蛸 ➡ 制酸 清理疮面

主成份CaCO3；现代研究证实具有止血、制酸及促进溃疡愈合作用，提高前列腺素尤其是PGE2的含量，抑制胃酸分泌；良好的吸附作用，吸附有毒素和细菌的血液与炎性渗出粘液

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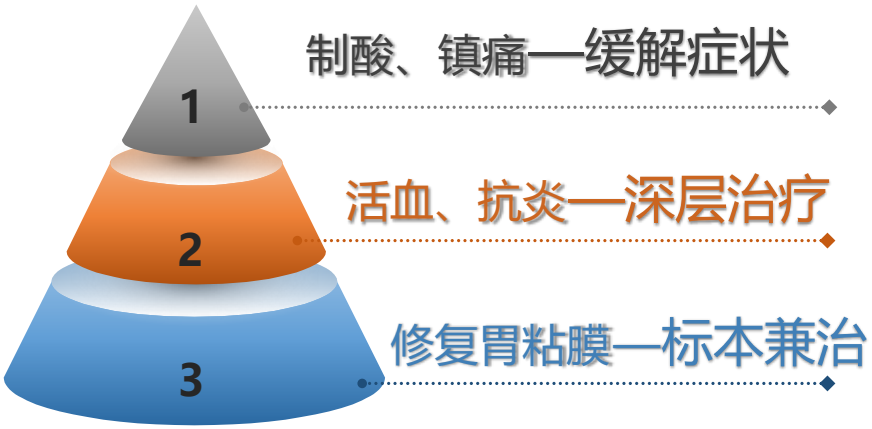
药理功效

甘海胃康治疗胃肠疾病三步曲



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诱导急性胃黏膜损伤模型

实验开始时禁食20小时

- 乙醇损伤组：80%乙醇，200ul灌胃，4小时后禁水禁食。连续处理3天后处死昆明鼠，解剖胃部，进行粘膜评估。
- 吲哚美辛组：吲哚美辛用5%NaHCO3溶解，200ul灌胃（20mg/kg），4小时后禁水禁食，连续处理3天处死昆明鼠，解剖胃部，进行粘膜评估。
- 阿司匹林组：阿司匹林用5% NaHCO3溶解，以200ul（200mg/kg），4小时内禁水禁食，连续处理3天，解剖胃部，进行粘膜评估。

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化学性损伤模型分组

- 正常组（8只）
- 乙醇组（8只）
- 乙醇+甘海胃康组（8只）
- 阿司匹林组（8只）
- 阿司匹林+甘海胃康组（8只）
- 吲哚美辛组（8只）
- 吲哚美辛+甘海胃康组（8只）

上述造模3天，评价胃部溃疡及出血状态，每组选择3只，最后5只用于统一实验。

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观察指标

- 根据Guth标准计算溃疡指数和抑制率
- 溃疡或糜烂面积计分：每3个点状溃疡（粘膜缺损<1mm或者出血点，称为点状溃疡），计1分；条状出血：以游标卡尺测量溃疡面的最大长径和垂直于最大长径的最大宽径，二者的乘积即为溃疡指数。
- 溃疡抑制率%=（损伤模型组溃疡指数-给药组溃疡指数）/损伤模型组溃疡指数。
- 血清IL-2, IL-8, TNF-a， NO, PGE2, IL-10的检测。

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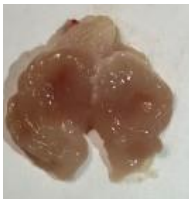
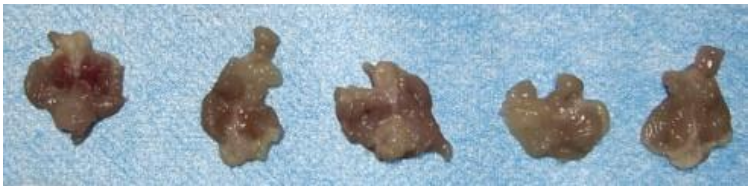
分组（Hp模型及治疗分组）

- 完全不处理的健康组 （12只）
- 生理盐水组 （12只）
- Hp组 （18只）
- 三联+Hp组 （18只）
- 四联+Hp组 （18只）
- 甘海胃康组 （18只）
- 三联+甘海胃康+Hp组 （18只）
- 四联+甘海胃康+Hp组 （18只）

Hp造模：标准菌株SS1 (来自北大医院），第1天用幽门螺杆菌悬液灌胃小鼠400ul/只,以后隔天灌胃1次,每次200uL/只,共5次。造模后4周，造模组各选3只，进行评价Hp的感染状态，再确认后，开始给予药物干预，间隔1天给药，每次200ul，连续给药6次，再牺牲小鼠观察。观察Hp：RUT检测，Hp抗原检测，银染实验，透射与扫描电镜观察组织结构变化。血清血清IL-2, IL-8, TNF-a， NO, PGE2, IL-10的检测。

正常胃





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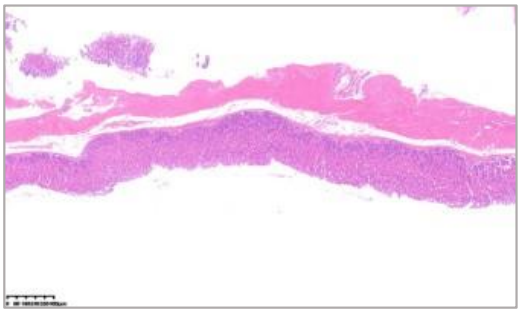

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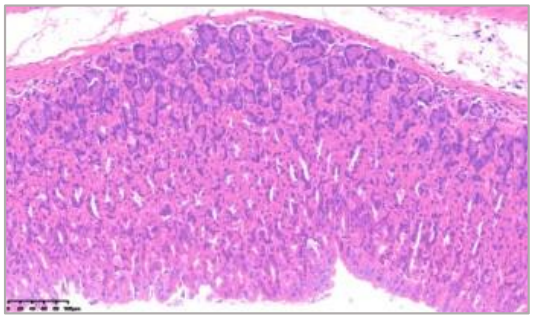

200x

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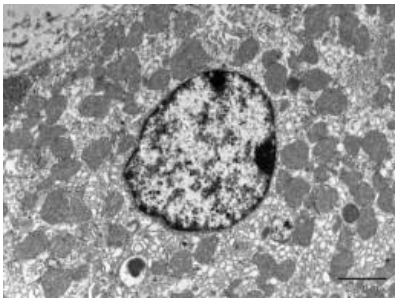
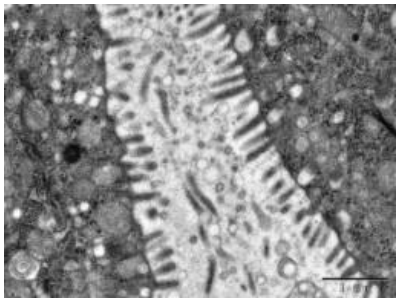
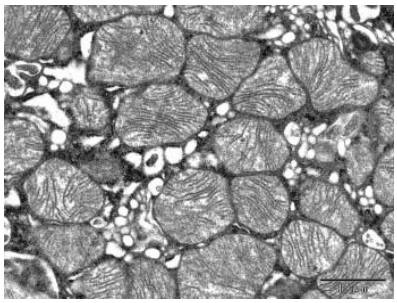
健康昆明鼠胃黏膜透射电镜图



整体细胞状态

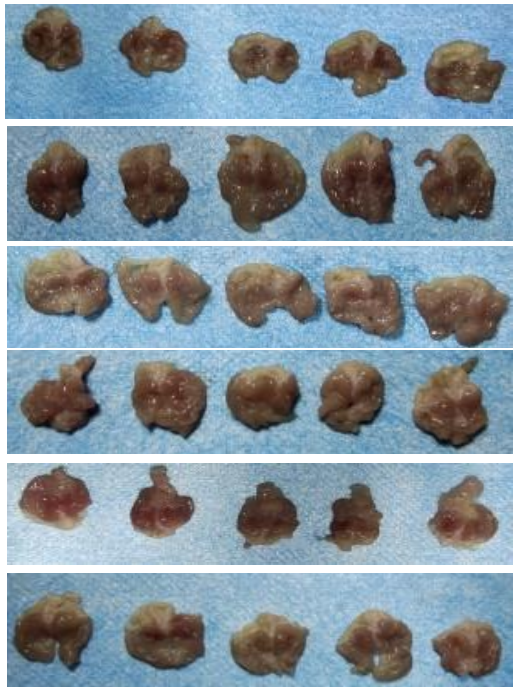


细胞微绒毛结构



线粒体结构

胃炎评分（出血+溃疡）满分5分



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各组大鼠溃疡指数和溃疡抑制率比较

组别	溃疡指数（面积，mm^2）	溃疡抑制率（%）
乙醇组	45.83 ±8.56	/
乙醇+甘海胃康组	24.49 ±5.17**	45.56
吲哚美辛组	32.32 ±6.87	/
吲哚美辛+甘海胃康组	14.16 ±5.33**	56.19
阿司匹林组	28.56 ±7.32	/
阿司匹林+甘海胃康组	11.55 ±8.58**	59.56

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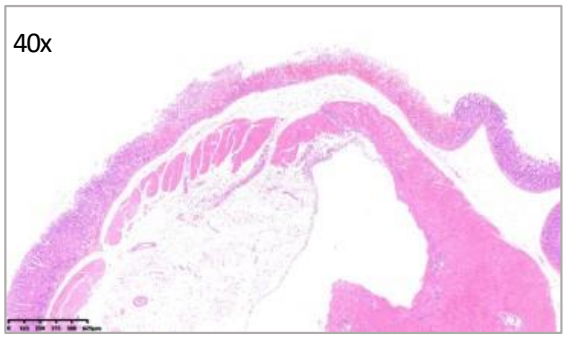
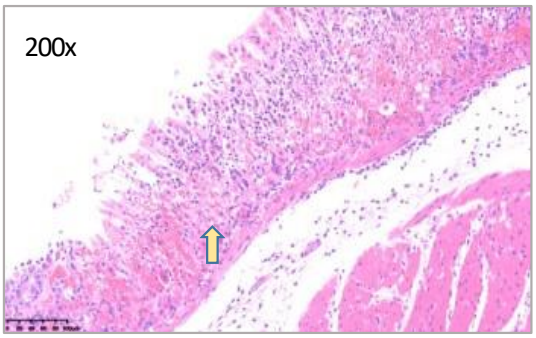
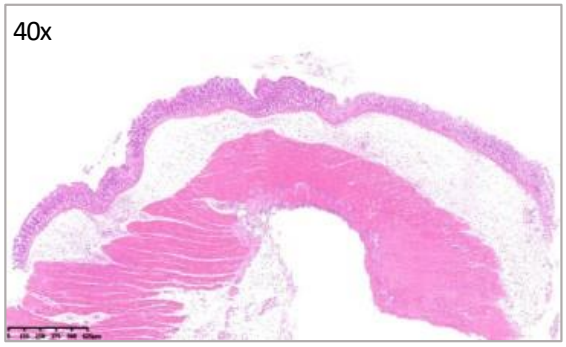
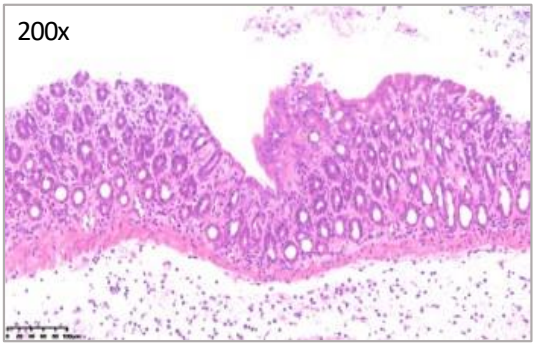
乙醇组





乙醇
+甘海胃康组





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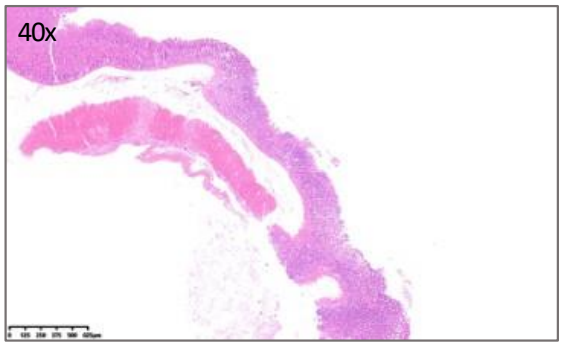
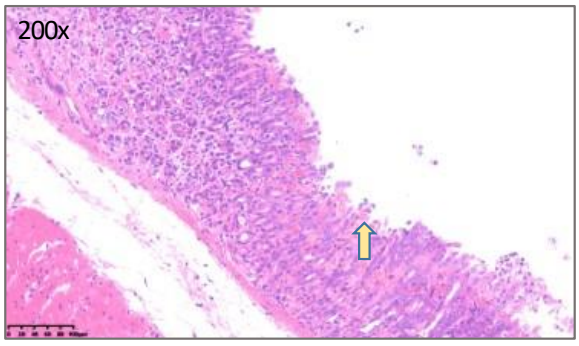
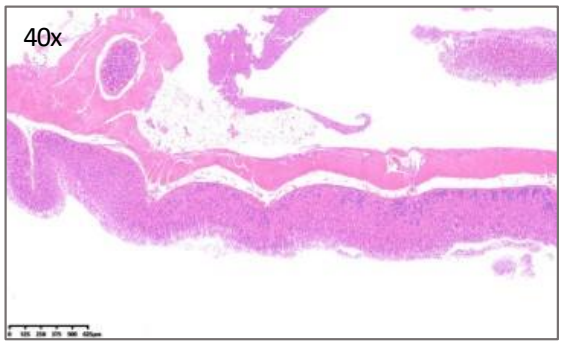
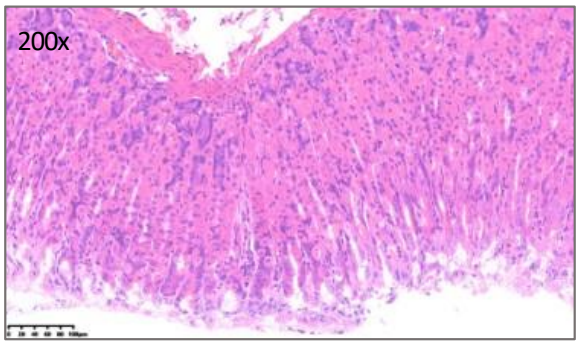
吲哚
美辛组





吲哚
美辛+
甘海
胃康组





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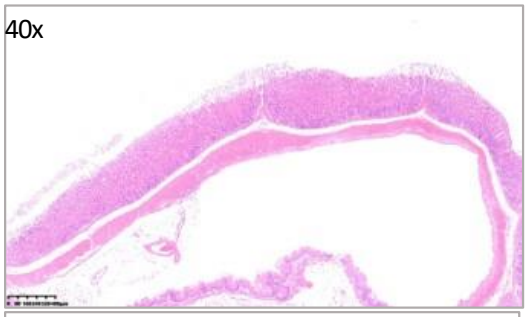
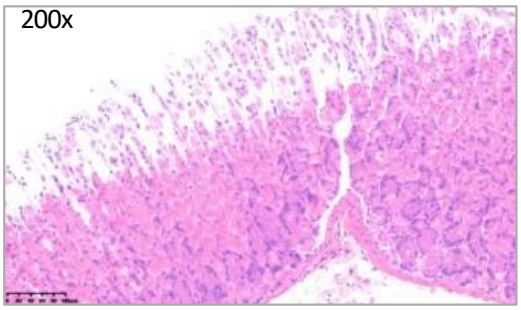
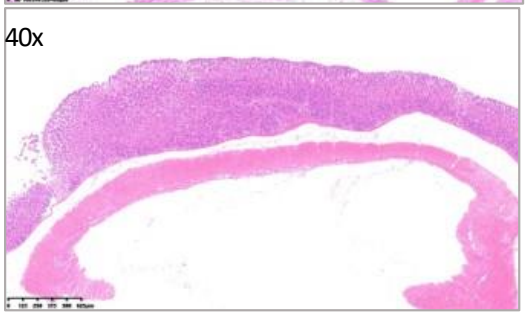
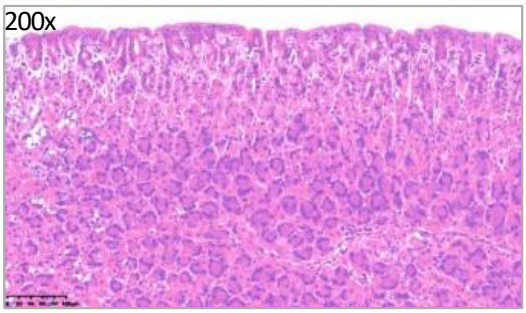
阿司匹林组





阿司匹林+
甘海胃康组





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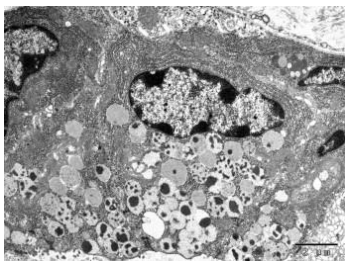
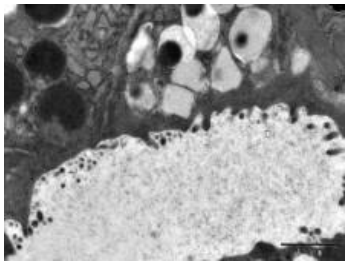
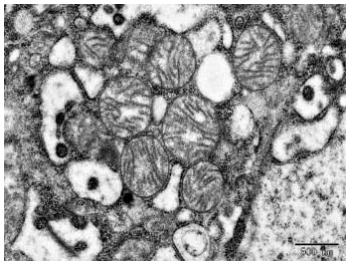
甘海胃康修复乙醇所致昆明鼠胃炎的胃黏膜透射电镜数据

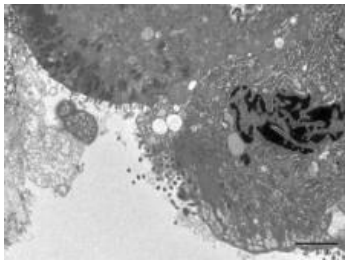
乙醇组

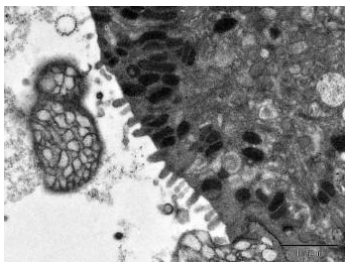


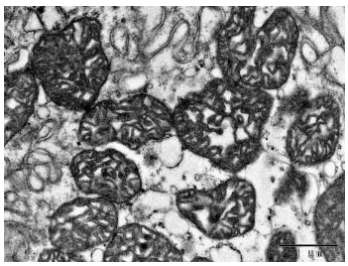




乙醇+
甘海胃康组







乙醇导致昆明鼠微绒毛结构消失，细胞核皱缩，胞浆内细胞器结构紊乱空泡化
甘海胃康在一定程度上可改善胃黏膜微绒毛和亚细胞器结构

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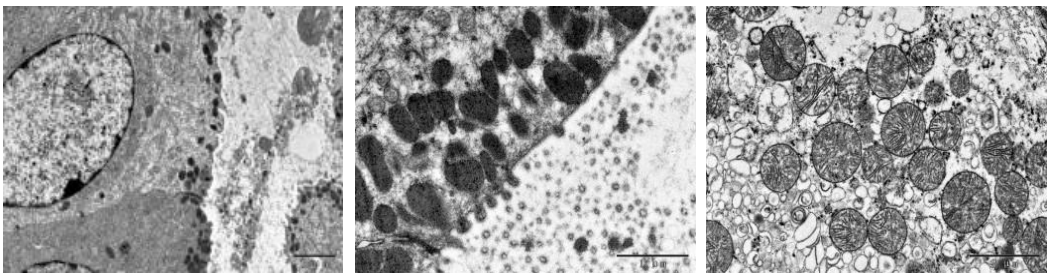
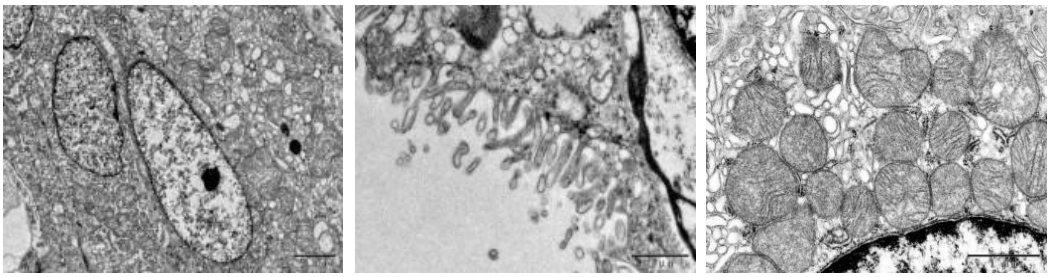
甘海胃康修复阿司匹林所致昆明鼠胃炎的胃黏膜透射电镜数据

阿司匹林组



阿司匹林
+甘海胃康组



阿司匹林导致昆明鼠微绒毛结构变短脱落，线粒体部分萎缩变小
甘海胃康在一定程度上改善胃黏膜微绒毛和线粒体亚细胞器结构

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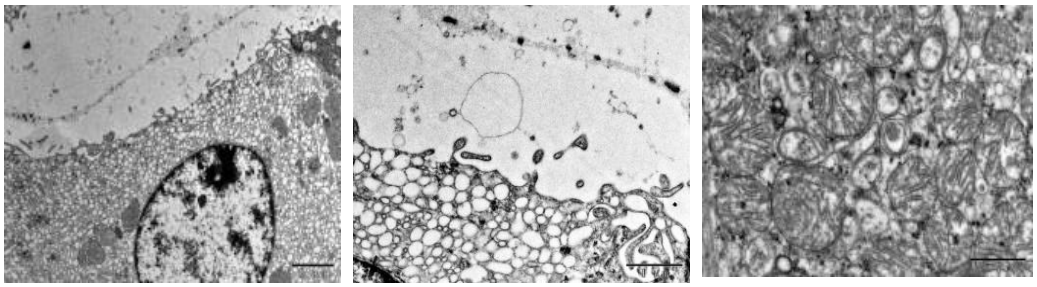
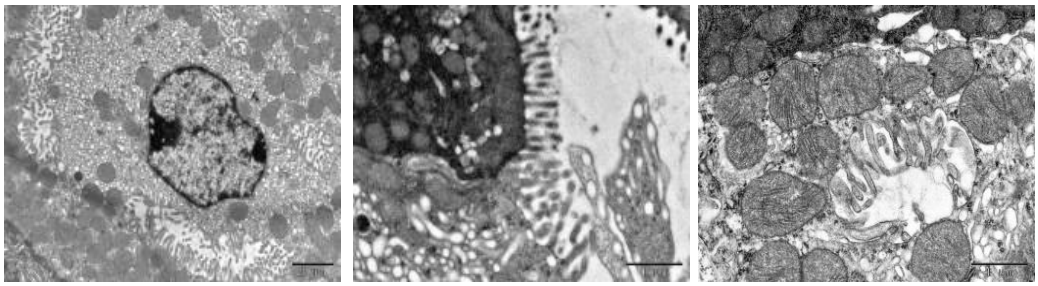
甘海胃康修复吲哚美辛所致昆明鼠胃炎的胃黏膜透射电镜数据

吲哚美辛组



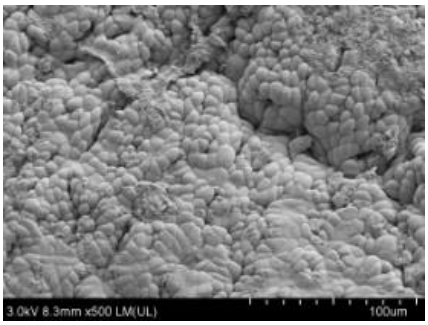
吲哚美辛组
+甘海胃康



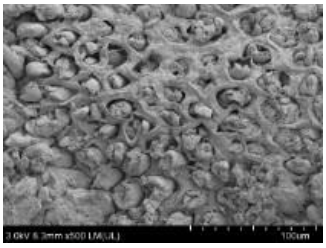
吲哚美辛导致昆明鼠微绒毛结构变短脱落，线粒体内嵴部分消失，肿胀
甘海胃康在一定程度上改善胃黏膜微绒毛和线粒体亚细胞器结构

甘海胃康修复乙醇/阿司匹林/吲哚美辛所致昆明鼠胃炎的胃黏膜扫射电镜数据

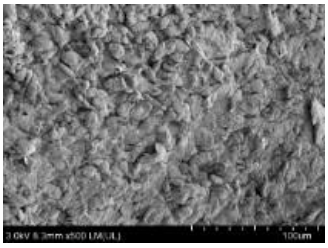
健康组



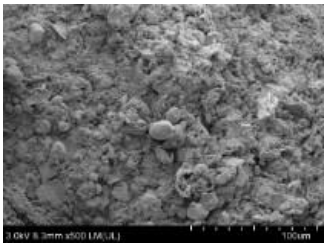
乙醇组



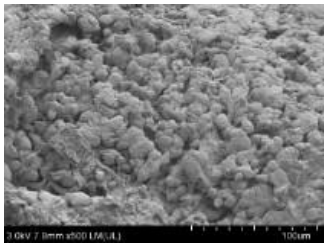
阿司匹林组



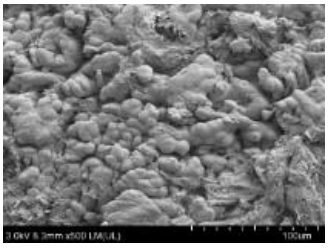
吲哚美辛组



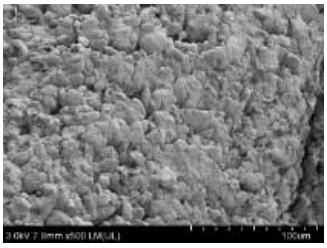
乙醇+甘海胃康组



阿司匹林+甘海胃康组



吲哚美辛+甘海胃康组



化学性诱导模型组小鼠血清中IL-2, IL-8, TNF-a， NO， PGE2的ELISA变化(单位：pg/mg）

组别	n	IL-2	IL-8	TNF-a	NO	IL-10	PGE2
正常组	5	37.65±3.27	14.23±4.56	7.88±3.55	43.56±7.34	11.53±4.87	823.41±351.98
乙醇组	5	13.21±3.08	43.26±7.54	142.45±45.56	10.52±3.45	115.42±55.21	123.56±56.79
乙醇+甘海胃康组	5	19.65±3.29*	34.32±5.63*	82.54±35.72*	18.45±5.87*	67.23±25.69*	322.45±147.72**
吲哚美辛组	5	24.21±3.49*	27.73±6.51	89.56±35.23	21.56±6.33	62.45±30.41	467.32±212.54
吲哚美辛+甘海胃康组	5	30.29±4.32**	19.22±5.12**	42.45±11.48**	34.53±10.45**	26.55±12.59**	635.68±259.33**
阿司匹林组	5	21.48±2.31	25.38±4.26	75.44±31.47	20.52±6.23	54.33±23.56	387.45±187.65
阿司匹林+甘海胃康组	5	28.22±1.67**	18.78±3.26**	34.65±15.86**	36.12±7.39**	31.46±18.65**	653.22±202.53**

*， p<0.05, **, p<0.01

Hp实验模型 快速尿素酶试验数据

RUT检测				
分组	阳性	阴性	阳性率	P-值
完全健康	0	12	0%	<0.001
生理盐水组	0	12	0%	<0.001
HP组	13	2	86.7%	/
三联+HP组	8	7	53.3%	0.109
四联+HP组	6	9	40%	0.021
甘海胃康+HP组	7	8	46.7%	0.050
三联+甘海胃康+HP组	4	11	26.7%	0.002
四联+甘海胃康+HP组	2	13	13.3%	<0.001

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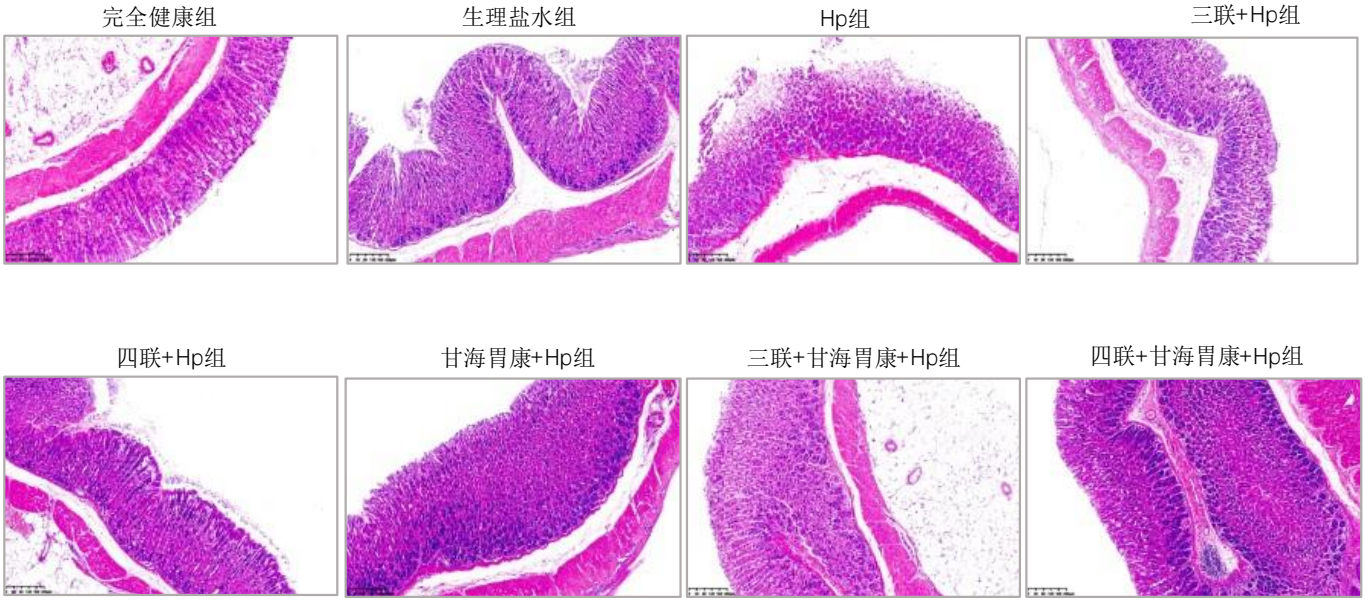
Hp实验模型 粪便Hp抗原试验数据

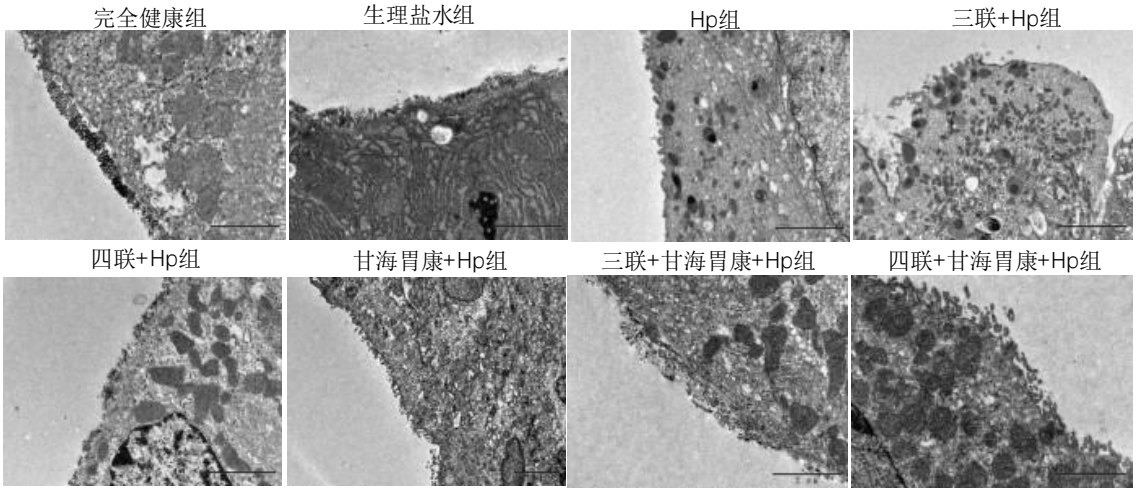
粪便Hp抗原检测				
分组	阳性	阴性	阳性率	P-值
完全健康组	0	12	0%	<0.001
生理盐水组	0	12	0%	<0.001
HP组	12	3	80%	/
三联+HP组	7	8	46.7%	0.128
四联+HP组	5	10	33.3%	0.025
甘海胃康+HP组	6	9	40.0%	0.060
三联+甘海胃康+HP组	3	12	20.0%	0.003
四联+甘海胃康+HP组	1	14	6.7%	<0.001

体重变化

组别	初始体重（g）	Hp造模后体重（g）	灌药后体重（g）	P-值
正常组	43.4±1.9	48.6±1.8	58.7±3.7	P<0.05
Saline组	42.3±2.8	47.2±3.2	56.2±2.9	P<0.05
Hp组	42.6±1.5	45.5±1.2	53.5±3.5	比较基线
三联组	43.2±2.7	45.4±3.1	54.0±3.4	P<0.05
四联组	42.8±2.2	46.0±2.4	55.3±4.5	P<0.05
甘海胃康组	42.4±2.9	45.6±2.9	56.8±3.6	P<0.05
三联+甘海胃康组	43.3±1.7	44.2±3.7	57.4±2.4	P<0.05
四联+甘海胃康组	43.1±2.3	45.9±1.5	57.8±6.3	P<0.05

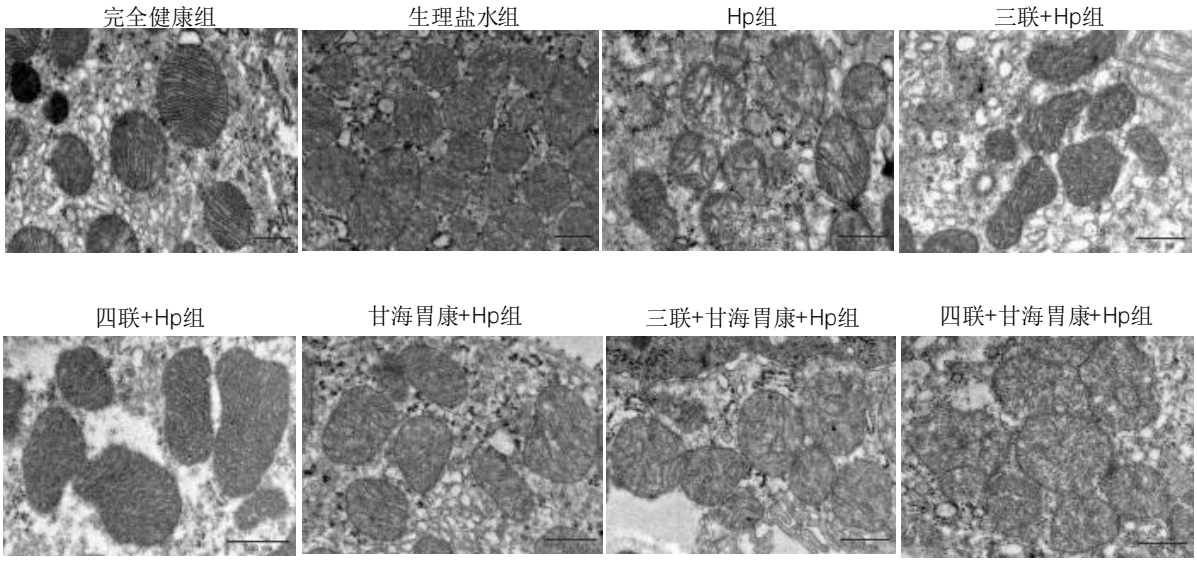


Hp实验各组胃黏膜微绒毛的透射电镜比较



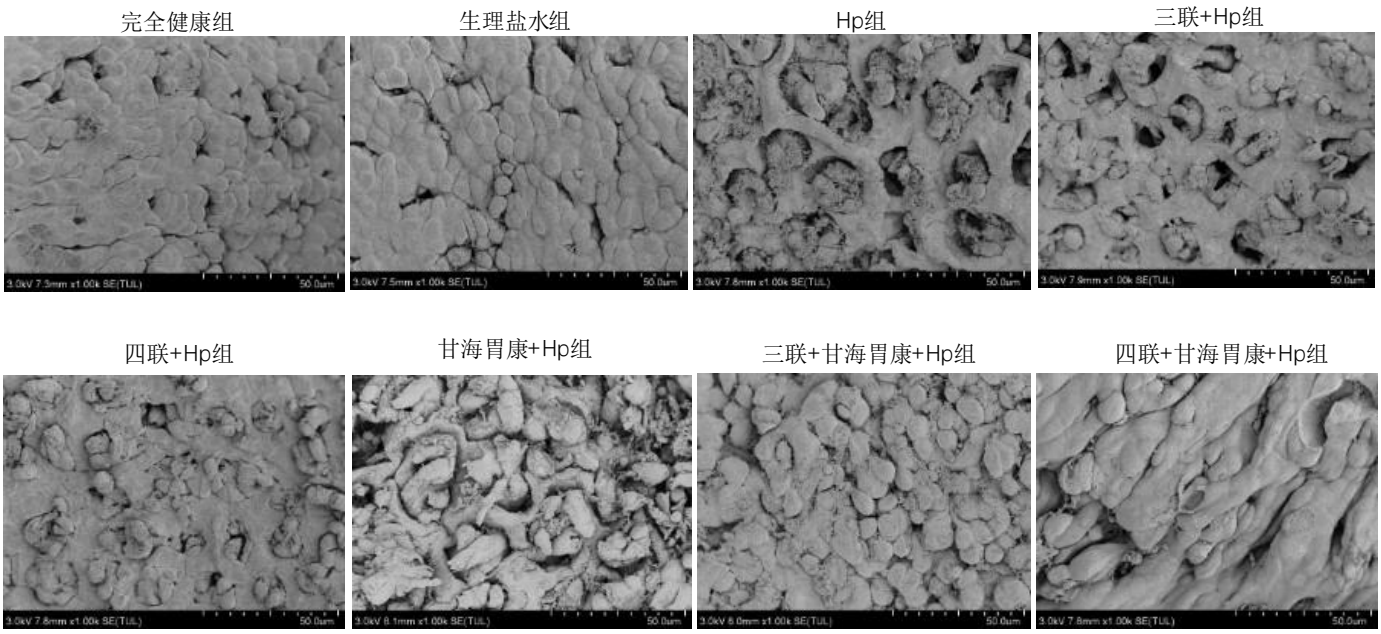
甘海胃康有一定的胃黏膜微绒毛的保护性作用

Hp实验各组胃黏膜线粒体结构的透射电镜比较



甘海胃康有一定的胃黏膜线粒体亚结构的保护性作用

Hp实验各组胃黏膜扫描电镜比较



甘海胃康对胃黏膜的保护作用和协同临床常规药物的治疗作用

各组小鼠IL-2, IL-8, TNF-a， NO, PGE2, IL-10的ELISA变化(单位：pg/mg）

组别	n	IL-2	IL-8	TNF-a	NO	IL-10	PGE2
正常组	12	38.45±4.54**	16.78±3.26**	7.45±2.43**	46.73±6.89**	12.23±3.68**	848.34±302.45**
Saline组	12	36.55±4.12**	18.93±5.33**	8.23±3.15**	42.56±8.55**	13.45±4.59**	793.45±353.17**
Hp组	15	19.65±3.29	31.55±6.78	57.54±8.59	15.56±3.58	36.73±7.33	342.13±135.52
三联组	15	26.88±5.39*	22.37±4.62*	40.45±4.12*	24.24±5.31*	26.54±4.47*	532.16±203.58*
四联组	15	24.21±3.67*	21.66±4.54*	35.22±5.62*	26.35±7.12*	24.33±4.81*	568.45±242.44*
甘海胃康组	15	28.34±4.27*	20.79±3.32*	30.21±5.86**	28.58±6.18*	22.56±6.35**	623.58±323.39**
三联+甘海胃康组	15	27.67±3.92*	19.56±4.02**	18.34±7.23**	30.59±7.38**	18.48±5.69**	669.34±367.41**
四联+甘海胃康组	15	26.63±2.18*	19.88±2.74**	16.55±5.62**	33.69±8.23**	17.34±6.12**	714.45±321.59**

*， p<0.05, **, p<0.01

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研究背景

课题设计

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1 甘海胃康可明显改善乙醇/阿司匹林/吲哚美辛所致昆明小鼠胃黏膜损伤。

2 甘海胃康对昆明小鼠幽门螺杆菌标准菌株SS1感染有明显治疗作用。

感谢各位专家！

Thank you

甘海胃康胶囊治疗慢性胃炎伴功能性消化不良的多中心临床研究总结

杜奕奇
上海长海医院消化内科
2021.11

研究背景

- **功能性消化不良**（Functional dyspepsia，FD）：存在一种或多种起源于胃十二指肠区域的消化不良症状，并且缺乏能解释这些症状的器质性、系统性或代谢性疾病，属于**功能性胃肠病**范畴

功能性消化不良的流行病学
《胃肠病学和肝病学杂志》2013, vol. 22, No.1

FD的治疗措施

- 胃排空延迟
- 胃肠动力减弱
- 内脏高敏感
- 幽门螺杆菌感染
- 炎症和免疫异常
- 精神心理因素

促动力药

抑酸药

根除Hp

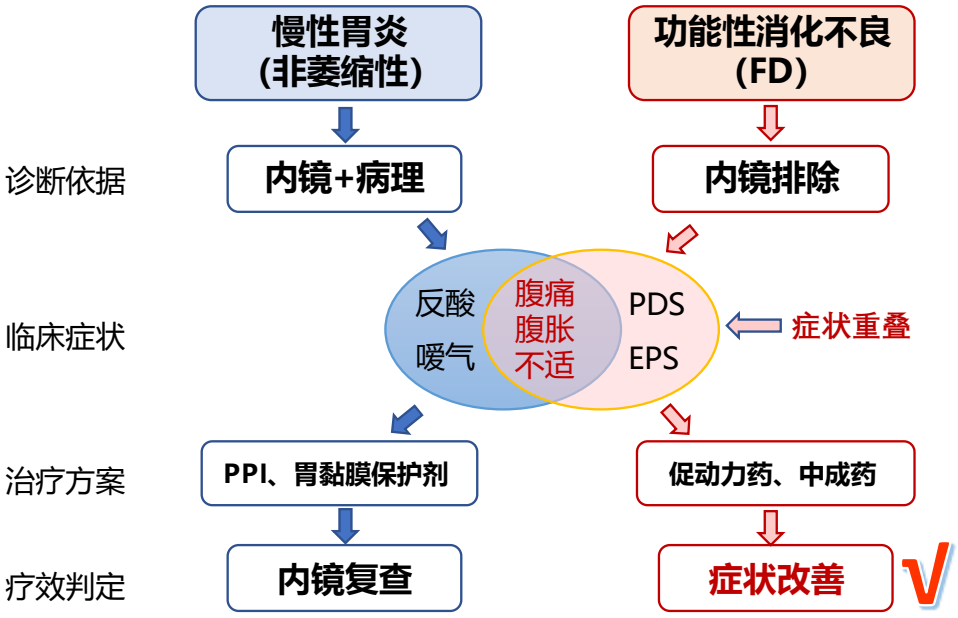
解痉药

抗抑郁药

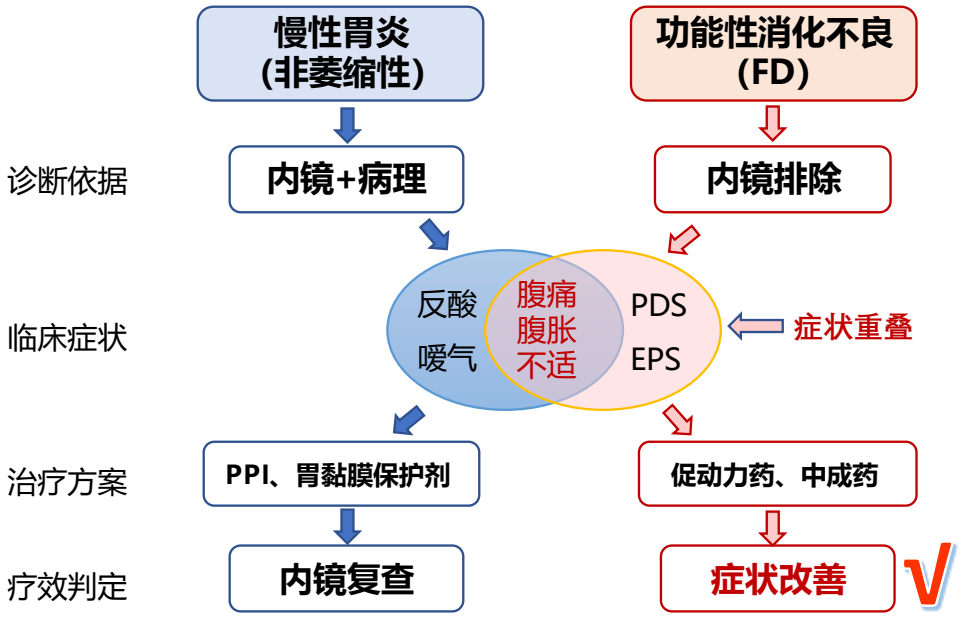
中 药

中医中药作为我国的传统医学，在治疗FD方面有独特功效

慢性胃炎与FD

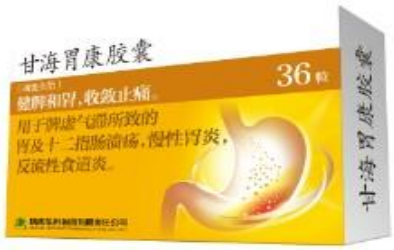


慢性胃炎与FD



甘海胃康胶囊

- 【通用名】：甘海胃康胶囊
- 【组　方】：甘草、海螵蛸、沙棘、枳实、白术、黄柏、延胡索、绞股蓝总苷
- 【规　格】： 0.4g*3粒/0.4g*6粒
- 【性　状】：本品为硬胶囊，内容物为棕色至棕褐色的颗粒和粉末；味微苦
- 【功能主治】：健脾和胃，收敛止痛。用于脾虚气滞所致的胃及十二指肠溃疡，慢性胃炎，反流性食道炎
- 【用法用量】：口服，一次6粒，一日3次
- 【批准文号】：Z20025708



甘海胃康的药理机制

组方及功效

组方	成分	功效
枳实	挥发油	增加胃肠运动收缩节律、调节免疫力
白术	苍术酮	双向调节胃肠系统、调节免疫力
甘草	甘草苷、甘草酸 甘草萜醇	双向调节胃肠作用，抗炎，抗溃疡
海螵蛸	碳酸钙	中和胃酸
绞股蓝	绞股蓝总苷	增加胃黏膜细胞新陈代谢， 促进肉芽组织生长和溃疡闭合
黄柏	小檗碱	广谱抗菌作用、可抑杀Hp
沙棘	维生素、氨基酸	抗自由基作用
延胡索	延胡索乙素 去氢延胡索甲素	镇痛、抗溃疡

甘海胃康的动物实验研究

长海医院 CHANGHAI HOSPITAL

药理研究

甘海胃康胶囊具有明显镇痛作用

组别	动物（n）	给药前动物痛阈时间（s）	给药后动物痛阈时间（s）	
			30min	60min
NS对照组	10	17.2±8.2	18.5±7.4	17.4±6.8
杜冷丁对照组	10	20.9±4.8	42.7±11.4**	53.0±16.8**
甘海胃康大剂量	10	18.7±6.46	28.1±17.1 **	46.7±19.2**
甘海胃康小剂量	10	21.8±7.2	29.2±5.6*	37.6±12.4**

*P ‹ 0.01 **P ‹ 0.001

西安交通大学医学院临床药理研究所

结论：甘海胃康大剂量组给药后动物痛阈时间和杜冷丁组相当，结果表明甘海胃康胶囊具有明显的镇痛作用

甘海胃康的动物实验研究

药理研究

甘海胃康对抗多种原因引起的溃疡

实验名称	观察指数	水对照组	甘海胃康小剂量组	甘海胃康中剂量组	甘海胃康大剂量组
束缚应激法	溃疡指数mm	23.91±9.66	14.41±7.11**	5.11±4.88 ***	6.66±8.15***
	抑制百分率		41%	79%	86%
消炎痛+乙醇	溃疡指数mm	17.70±11.30	5.52±4.41***	8.81±9.32 *	8.30±9.00*
	抑制百分率		41%	80%	85%
HCl损伤	溃疡指数mm	44.50±28.96	8.33±7.46**	5.10±4.56 ***	4.80±3.27***
	抑制百分率		81%	89%	89%

*P < 0.01 **P < 0.001

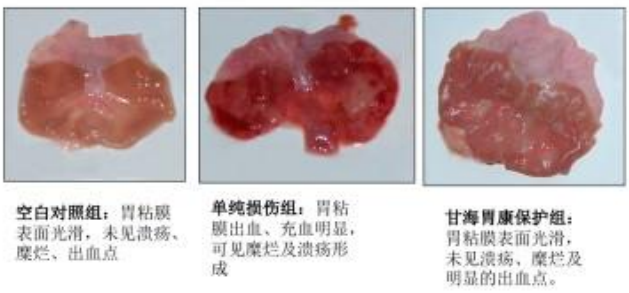
西安交通大学医学院临床药理研究所

结论：甘海胃康对束缚应激法、消炎痛+乙醇、盐酸损伤等原因所致溃疡具有对抗作用

甘海胃康的动物实验研究

药理研究

甘海胃康预防小鼠胃黏膜损伤



空白对照组：胃粘膜表面光滑，未见溃疡、糜烂、出血点

单纯损伤组：胃粘膜出血、充血明显，可见糜烂及溃疡形成

甘海胃康保护组：胃粘膜表面光滑，未见溃疡、糜烂及明显的出血点。

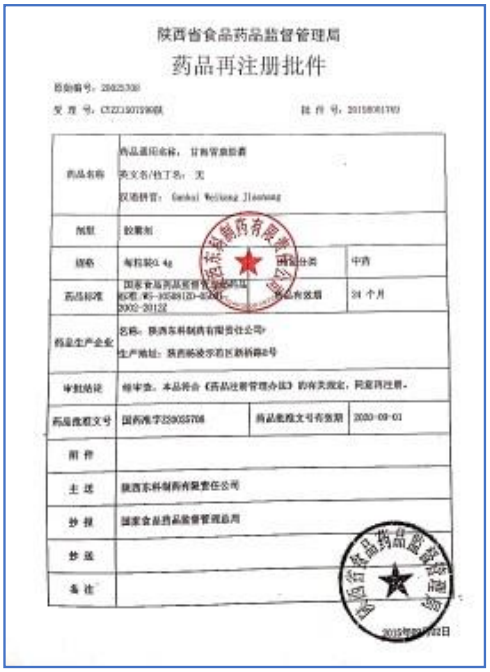
组别	损伤指数（UI）
正常对照组	3.60±1.24
单纯损伤组	61.3±12.4
硫糖铝组	15.2±7.93
甘海胃康组	18.7±13.6

西安交通大学医学院临床药理研究所

结论：甘海胃康可以减轻乙醇所致大鼠胃黏膜损伤，其预防作用与硫糖铝作用相当

甘海胃康胶囊临床研究

甘海胃康胶囊治疗慢性胃炎伴功能性消化不良的随机、双盲、安慰剂平行对照的多中心临床研究


陕西省食品药品监督管理局

药品再注册批件

研究参加单位

序号	参研单位	研究者
1	海军军医大学第一附属医院	李兆申 杜奕奇
2	首都医科大学附属北京中医医院	张声生
3	山东大学齐鲁医院	李延青
4	浙江大学附属第一医院	季　峰
5	中南大学湘雅三院	王晓艳
6	天津市中医药研究院附属医院	刘华一
7	黑龙江省中医科学院	潘　洋

研究周期：2017年8月-2020年4月

项目研究历程

2017.08.13 通过上海长海医院伦理委员会审批，获取伦理批件

2018.01.15 方案论证会暨项目启动会于上海召开，确立项目研究方案

2018.03.20 项目中期协调会在济川药业召开

2018.06.16 长海医院启动第一例病例入组，各分中心陆续启动病例入组

2020.04.12 完成最后一例病例入组，共纳入324例

2020.11.15 项目完成数据统计及揭盲工作，总结会于上海顺利召开

启动会
2017.08.13

中期会
2018.06.16

总结会
2020.11.15

研究方案

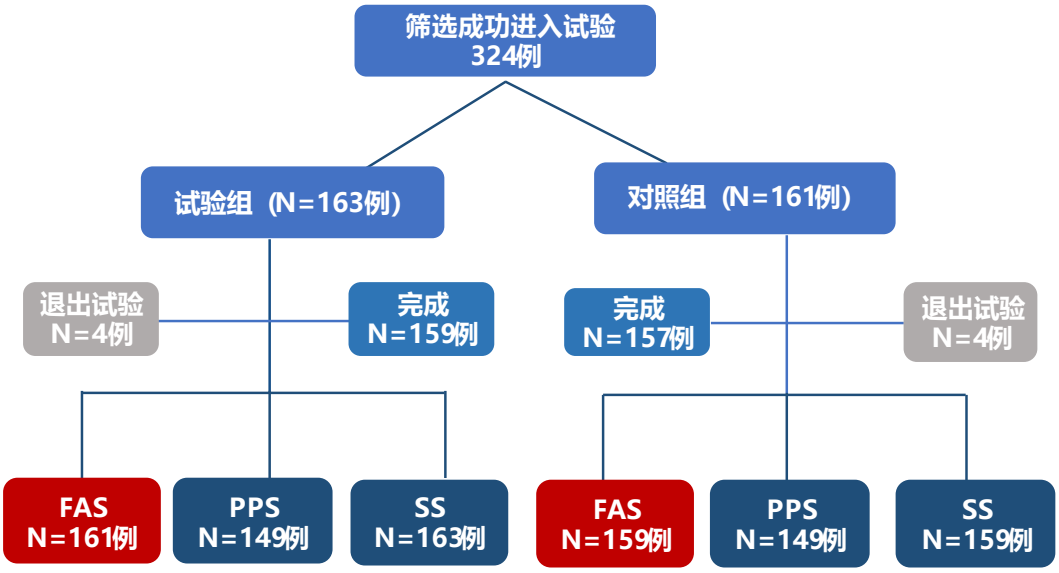
- **用药方案：**

试验组：甘海胃康胶囊（A组）6粒/次，3次/日，饭前口服；
对照组：安慰剂（B组）6粒/次，3次/日，饭前口服；

- **试验周期：**筛选期 3 天（**访视2**）、双盲试验期 4 周（**访视3-5**）、随访期2周（**访视6**）

国药准字	药物编号：
甘海胃康胶囊临床研究用药	
（仅供临床研究使用）	
【功能主治】	健脾和胃，收敛止痛。用于脾虚气滞所致的胃及十二指肠溃疡，慢性胃炎，反流性食道炎。
【规　格】	每粒装0.4g
【用法用量】	口服一次6粒，一日3次。
【贮藏方法】	密闭，置阴凉处（不超过20℃）
【批　号】	
【有 效 期】	24个月
陕西东科制药有限责任公司提供	
请在治疗结束时交还所有剩余药物和空药盒给药物保管员	

研究流程



研究结果

表1.1　两组脱落、剔除率的比较

组别	入组数	脱落/剔除数	脱落/剔除率（%）	检验方法	统计量	P值
甘海胃康	163	14	8.59	卡方检验	0.14	0.7068
安慰剂	161	12	7.45			

研究结果

中心	组别	入组数	完成数	脱落数	脱落率(%)	剔除数	剔除率(%)
上海长海医院	A组	20	18	2	10.00	2	10.00
上海长海医院	B组	21	21	0	0.00	0	0.00
上海长海医院	合计	41	39	2	4.88	2	4.88
山东大学齐鲁医院	A组	22	22	0	0.00	0	0.00
山东大学齐鲁医院	B组	18	18	0	0.00	0	0.00
山东大学齐鲁医院	合计	40	40	0	0.00	0	0.00
浙江大学附属第一医院	A组	9	9	0	0.00	0	0.00
浙江大学附属第一医院	B组	11	9	2	18.18	2	18.18
浙江大学附属第一医院	合计	20	18	2	10.00	2	10.00
天津市中医药研究院附属医院	A组	41	41	0	0.00	2	4.88
天津市中医药研究院附属医院	B组	40	40	0	0.00	0	0.00
天津市中医药研究院附属医院	合计	81	81	0	0.00	2	2.47
黑龙江省中医院	A组	57	57	0	0.00	2	3.51
黑龙江省中医院	B组	58	58	0	0.00	0	0.00
黑龙江省中医院	合计	115	115	0	0.00	2	1.74
中南大学湘雅三院	A组	4	3	1	25.00	1	25.00
中南大学湘雅三院	B组	4	2	2	50.00	0	0.00
中南大学湘雅三院	合计	8	5	3	37.50	1	12.50
首都医科大学附属北京中医医院	A组	10	9	1	10.00	6	60.00
首都医科大学附属北京中医医院	B组	9	9	0	0.00	8	88.89
首都医科大学附属北京中医医院	合计	19	18	1	5.26	14	73.68
合计	**A组**	**163**	**159**	**4**	**2.45**	**13**	**7.98**
合计	**B组**	**161**	**157**	**4**	**2.48**	**10**	**6.21**
合计	**合计**	**324**	**316**	**8**	**2.47**	**23**	**7.10**

研究结果

表2 各中心数据集情况

中心	FAS分析集		
	甘海胃康	安慰剂	合计
上海长海医院	18	21	39
山东大学齐鲁医院	22	18	40
浙江大学附属第一医院	9	9	18
天津市中医药研究院附属医院	41	40	81
黑龙江省中医院	57	58	115
中南大学湘雅三院	4	4	8
北京中医医院	10	9	19
合计	161	159	320

研究结果

基线分析

入组时两组间的性别分布、年龄、治疗史、过敏史例数分布、合并疾病的差异均无统计学意义(P>0.05)。

项目		试验组	对照组	检验方法	P值
性别	男性	67例(41.61%)	76例(47.80%)	卡方检验	0.251
	女性	94例(58.39%)	83例(52.20%)		
平均年龄(岁)		45.89(11.90)	45.69岁	秩和检验	0.9052
治疗史		37例(22.98%)	37例(23.27%)	卡方检验	0.9511
曾有过敏史		5例(3.11%)	5例(3.14%)	校正卡方检验	1.000
合并疾病		2例(1.24%)	4例(2.52%)	校正卡方检验	0.6689

研究结果

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入组时两组间的性别分布、年龄、治疗史、过敏史例数分布、合并疾病的差异均无统计学意义(P>0.05)。

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曾有过敏史		5例(3.11%)	5例(3.14%)	校正卡方检验	1.000
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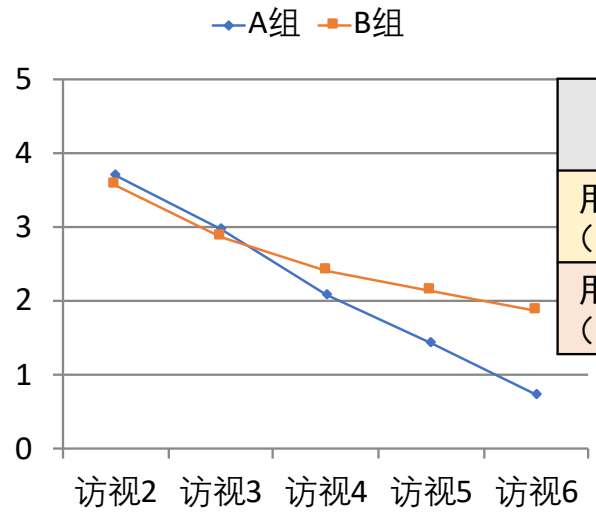
研究结果

次要疗效指标

治疗前后两组消化道症状（**早饱**）评分变化情况-FAS

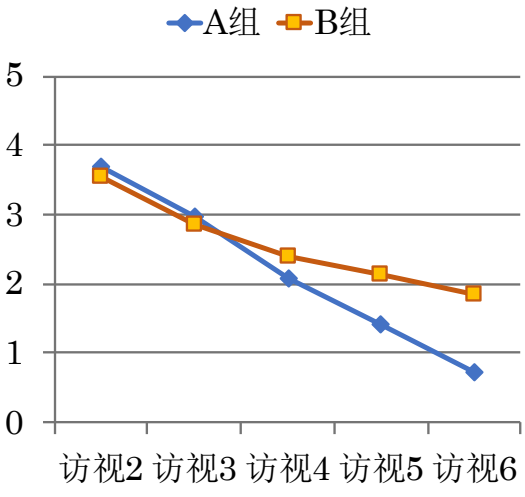


早饱积分	甘海胃康	模拟剂
用药前（访视2）	3.34±2.31	3.31±2.20
用药后（访视6）	0.80±1.24	1.65±1.63

研究结果

次要疗效指标

治疗前后两组消化道症状（**上腹痛**）评分变化情况-FAS

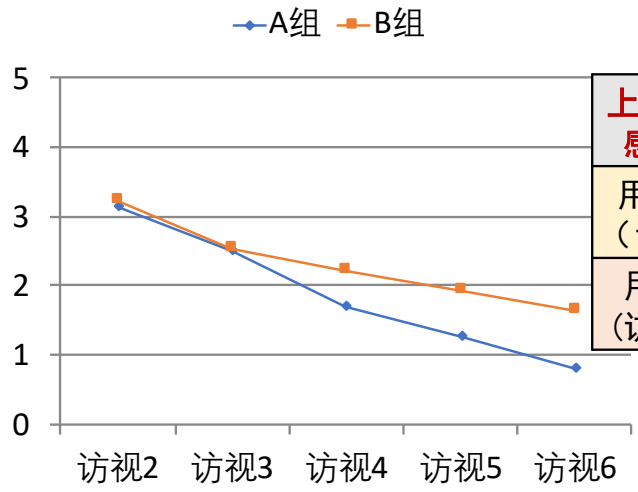


上腹痛积分	甘海胃康	模拟剂
用药前（访视2）	3.68±1.97	3.55±1.90
用药后（访视6）	0.71±1.08	1.86±1.58

研究结果

次要疗效指标

治疗前后两组消化道症状（**上腹烧灼感**）评分变化情况FAS



上腹烧灼感积分	甘海胃康	模拟剂
用药前（访视2）	3.15±2.21	3.21±2.03
用药后（访视6）	0.79±1.31	1.63±1.56

研究结果

两组治疗前后FD症状积分变化比较

时间截点	项目	FAS		PPS	
		试验组	对照组	试验组	对照组
	N(Missing)	161(0)	159(0)	149(0)	149(0)
访视点2（基线）	症状总积分	14.21(5.56)	14.21(5.60)	13.81(5.17)	14.11(5.56)
	P值	0.8082		0.5984	
访视点3（用药1周）	症状总积分	11.83(5.19)	11.23(4.80)	11.40(4.74)	10.92(4.53)
	P值	0.9749		0.4668	
访视点4（用药2周）	症状总积分	8.45(3.83)	9.53(4.35)	8.27(3.74)	9.23(4.06)
	P值	0.0032		0.0306	
访视点5（用药3周）	症状总积分	5.91(3.57)	8.47(4.32)	5.84(3.52)	8.21(4.19)
	P值	<0.0001		<0.0001	
访视点6（用药4周）	症状总积分	3.64(3.52)	7.37(4.26)	3.66(3.43)	7.13(4.15)
	P值	<0.0001		<0.0001	

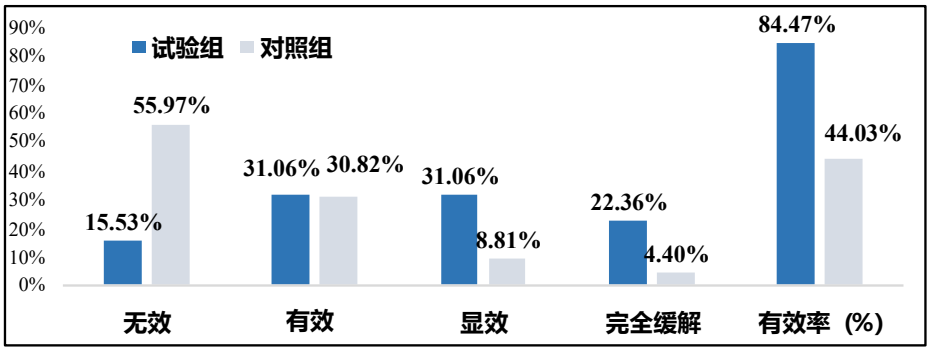
试验组的症状改善2周后与安慰剂效应脱离，并持续至4周以上

研究结果

主要疗效指标

用药4周后两组临床总有效率—FAS

组别	例数	无效	有效			有效率（%）
			有效	显效	完全缓解	
试验组	161	25	50	50	36	84.47%
对照组	159	89	49	14	7	44.03%

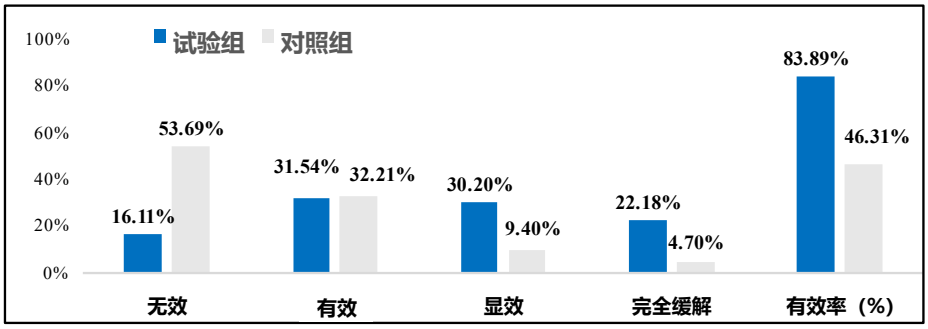


研究结果

主要疗效指标

用药4周后两组临床总有效率—PPS

组别	例数	无效	有效			有效率（%）
			有效	显效	完全缓解	
试验组	149	24	47	45	33	83.89%
对照组	149	80	48	14	7	46.31%



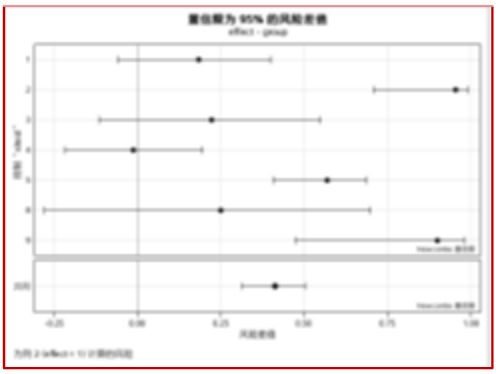
研究结果

表7.1　各中心临床总有效率的情况-FAS

中心	组别	无效	有效			有效率（%）	合计
			进步	显效	完全缓解		
1	A组	1	7	5	5	17(94.44)	18
	B组	5	7	5	4	16(76.19)	21
2	A组	1	5	14	2	21(95.45)	22
	B组	18	0	0	0	0(0.00)	18
3	A组	0	2	4	3	9(100.00)	9
	B组	2	7	0	0	7(77.78)	9
4	A组	18	13	3	7	23(56.10)	41
	B组	17	18	4	1	23(57.50)	40
5	A组	4	23	19	11	53(92.98)	57
	B组	37	15	4	2	21(36.21)	58
8	A组	0	0	1	3	4(100.00)	4
	B组	1	2	1	0	3(75.00)	4
9	A组	1	0	4	5	9(90.00)	10
	B组	9	0	0	0	0(0.00)	9
合计	A组	25	50	50	36	136(84.47)	161
	B组	89	49	14	7	70(44.03)	159

研究结果

图1.1　各中心临床总有效率比较的优效性检验森林图-FAS



- 经logistic 回归检验，通过对比包含与不包含中心与组别交互作用项的两个模型的对数似然函数值，得$\chi2=72.53$，df=6，$P<0.0001$，即交互作用项有统计学意义，故认为中心间差异有统计学意义
- 经扣除中心效应的CMH检验得，各中心汇总数据分析得出，两组率差（A组-B组）的95%CI下限为0.3161（Mantel-Haenszel法）、0.3333（Minimum Risk法）、0.3125（Newcombe法）、0.3118（Newcombe (MR)法），高于试验预设的优效性界值$\delta=0.07$

研究结果

安全性分析

组别	不良事件名称	严重程度	是否符合严重不良事件	纠正治疗	对研究药物的影响	转归	与研究药物的关系	因不良事件而退出试验	是否有严重不良事件
甘海胃康组	便秘	轻度	否	否	剂量不变	稳定	可能有关	否	否

不良反应分析：

甘海胃康组发生1 例轻度便秘，发生率为0.61%

安慰剂组发生0 例，发生率为0.00%，两组不良事件发生率差异无统计学意义（P=1.0000）。

研究结果

合并用药情况

表10 两组合并用药情况及比较—SS

组别	合计	有合并用药	合并用药发生率（%）	检验方法	统计量	P值
A组	163	4	2.45	校正卡方检验	0.00	1.0000
B组	159	4	2.52			

表10.1 合并用药详细情况—SS

中心	药物编号	组别	入组时间	药物名称	用法用量	合并用药目的	其他	开始时间	结束时间
上海长海医院	10	2	2018-08-06	百消丹	5g/次，2次/日	其他	乳腺增生	2018-07-30	2018-08-30
上海长海医院	10	2	2018-08-06	头孢呋辛酯片	2片/次，2次/日	其他	呼吸道感染	2018-08-09	2018-08-15
上海长海医院	10	2	2018-08-06	左氧氟沙星	1片/次，2次/日	其他	呼吸道感染	2018-08-09	2018-08-15
上海长海医院	11	1	2018-08-07	感冒冲剂	1包/次，3次/日	其他	上呼吸道感染	2018-08-28	2018-08-30
上海长海医院	14	1	2018-09-04	速立菲	1片/日	其他	缺铁	2018-08-26	2018-09-27
上海长海医院	24	1	2018-11-15	左氧氟沙星胶囊	0.1g/次，2次/日	其他	尿路感染	2018-12-01	2018-12-07

研究结果

合并用药情况

中心	药物编号	组别	入组时间	药物名称	用法用量	合并用药目的	其他	开始时间	结束时间
上海长海医院	24	1	2018-11-15	宁必泰胶囊	4粒/次，3次/日	其他	尿路感染	2018-12-01	2018-12-07
上海长海医院	24	1	2018-11-15	左氧氟沙星胶囊	0.1g/次，2次/日	其他	尿路感染	2018-12-18	2018-12-24
上海长海医院	28	2	2018-12-12	开瑞坦	1片/日	其他	过敏（荨麻疹）	2018-12-17	2018-12-31
上海长海医院	29	2	2018-12-19	柏尔克	2片/天	其他	上呼吸道感染	2019-01-06	2019-01-11
上海长海医院	38	2	2019-03-20	缬沙坦	1粒/日	其他	高血压	2011-UK-UK	2019-04-30
上海长海医院	38	2	2019-03-20	瑞舒伐他汀钙片	1片/日	其他	高血脂	2018-11-UK	2019-04-30
上海长海医院	40	1	2019-03-25	地奥司明片	0.9g/次，3次/日	其他	膝半月板损伤	2019-03-25	2019-04-08
上海长海医院	40	1	2019-03-25	氨基葡萄糖胶囊	942mg/次，3次/日	其他	膝半月板损伤	2019-03-25	2019-04-08
上海长海医院	40	1	2019-03-25	藤黄健骨片	3g/次，3次/日	其他	膝半月板损伤	2019-03-25	2019-04-08

研究结论

多中心临床研究表明：

口服甘海胃康胶囊治疗伴有消化不良症状的慢性胃炎 4周的临床总有效率高达84.5%，显著优于安慰剂的44％，用药2周后差异出现统计学意义。并且对于次要疗效指标上腹痛 餐后饱胀、早饱、上腹烧灼感的症状积分缓解，甘海胃康胶囊显著优于安慰剂。两种药物不良反应发生率比较差异无统计学意义。

甘海胃康胶囊是治疗慢性胃炎伴功能性消化不良有效而安全的药物。

甘海胃康用于慢性胃炎治疗

·3060· 中华中医药杂志(原中国医药学报)2017年7月第32卷第7期 CJTCMP, July 2017, Vol. 32, No. 7

·标准与规范·

慢性胃炎中医诊疗专家共识意见（2017）

中华中医药学会脾胃病分会

通讯作者：张声生[1]，唐旭东[2]

（[1]首都医科大学附属北京中医医院消化中心，北京 100010；[2]中国中医科学院西苑医院消化内科，北京 100091）

慢性胃炎伴胃黏膜充血、糜烂时，可加用中药三七粉、白及粉、珍珠粉治疗（随汤药冲服或用温水调成糊状口服，空腹时

5.15 甘海胃康胶囊 健脾和胃，收敛止痛。用于脾虚气滞所致的胃及十二指肠溃疡、慢性胃炎、反流性食管炎。

·1166· 中医杂志 2017 年 7 月第 58 卷第 13 期 Journal of Traditional Chinese Medicine, 2017, Vol. 58, No. 13

DOI:10.13288/j.11-2166/r.2017.13.023

标准与规范

胃脘痛中医诊疗专家共识意见（2017）

中华中医药学会脾胃病分会

4.4 中成药运用

4.4.1 气滞胃痛颗粒 舒肝理气，和胃止痛。用于肝郁气滞，胸痞胀满，胃脘疼痛。

4.4.16 甘海胃康胶囊 健脾和胃，收敛止痛。用于脾虚气滞所致的胃及十二指肠溃疡，慢性胃炎，反流性食管炎。

中药治疗FD/慢性胃炎的优势

- FD的症状较为复杂、重叠，单一机制的西药难以控制全部症状
- FD属于“心身疾病”范畴，受心理精神因素影响大（安慰剂效应高）
- FD的症状较为符合中医的“辩证施治”理念
- 中药的混合组方特点适用于FD复杂症状的治疗
- 中成药治疗FD服用方便，副作用小，易于推广

樊代明

中国工程院院士

- ✧中国工程院院士、美国医学科学院外籍院士
- ✧现任第十三届全国人大教科文卫委员会委员、中国抗癌协会理事长、亚太消化学会主席、国际抗癌联盟常务理事、世界消化学会常务理事、空军军医大学西京消化病医院院长、肿瘤生物学国家重点实验室主任、国家消化疾病临床医学研究中心主任、国家新药临床试验机构主任
- ✧曾任中国工程院副院长、第四军医大学校长、中华消化学会主任委员、国家科技奖励委员会委员、国家教材委员会委员
- ✧中国共产党十四大代表、第十一届和十三届全国人大代表、全国优秀共产党员、全国优秀科技工作者

封国生

北京医学会

- ✧主任医师、教授、博士生导师
- ✧北京医学会会长
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- ✧曾历任北京世纪坛医院院长、北京朝阳医院党委书记、理事长、北京市医院管理局党委书记、局长

朱建华

湖南省医学会

✧湖南省医学会副会长

✧湖南省医学会秘书长

刘新民

北京大学第一医院

- ✧教授、主任医师、博士生导师
- ✧现任北京大学第一医院 院长
- ✧历任北京大学第一医院党委书记
- ✧中国老年呼吸与危重症学会副主任委员
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- ✧《中华老年医学杂志》、《中华医学》等杂志编委

张欣

中南大学湘雅医院

✧教授、一级主任医师、博士生导师

✧现任中南大学湘雅医院党委书记

✧历任中南大学医院管理处处长兼湘雅医学院副院长，中南大学湘雅医院科研部主任

✧长期从事耳鼻咽喉头颈肿瘤以及咽喉嗓音医学研究、2000 年至 2006 年分别在美国德州大学 MD Anderson 癌症中心、匹兹堡大学肿瘤研究所、Emory 大学肿瘤研究所从事头颈肿瘤研究工作，2011 年 2 月-5 月在美国耶鲁大学从事医学伦理学研究

✧主持国家 863 项目 1 项、国家重大新药创制项目 1 项、国家社科基金重大项目 1 项、国家自然科学基金 5 项、参与主持医学伦理学重大国际合作项目 2 项等 16 项科研项目；发表 SCI 论文 54 篇

张澍田

北京友谊医院

- 现任首都医科大学附属北京友谊医院执行院长、消化分中心主任、主任医师、教授、博士生导师、现任世界华人消化医师协会会长、世界消化内内镜学会指导委员会委员、亚太消化内镜学会委员、中华医学会消化内镜学分会前任主任委员、中国医师协会消化医师分会会长、中华医学会消化病学分会前任副主任委员、北京医学会消化病学分会候任主委、北京医学会消化内镜学分会前任主委。
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- ✧ 毕业于原第四军医大学临床医学系，从事临床和医疗卫生管理 40 多年
- ✧ 曾先后担任军医，主治医师，副主任医师，主任医师，原第二炮兵卫生部医疗处处长，卫生部部长

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- ✧编审、高级策划编辑师
- ✧从事医学编辑出版工作 30 余年，曾担任人民卫生出版社医学教育出版中心副主任、医学学术中心主任
- ✧在医学教材、医学学术专著的编辑出版方面有较丰富的经验，策划编辑过《实用内科学》《黄宛临床心电图学》《实用检验医学》《临床检验操作规程》《老年医学》等数百部医学专著和教材
- ✧获得过第七届中华优秀出版物奖提名奖、第三届中华优秀出版物奖、年度中国书刊发行业协会全行业优秀畅销品种、年度中国书刊发行业协会全行业优秀畅销品种、卫生部优秀教材一等奖、第九届全国优秀科技图书奖暨科技进步二等奖、全国优秀学术期刊一等奖等

张万岱

南方医科大学南方医院

- ✧南方医科大学南方医院消化病研究所博士生导师、教授、主任医师
- ✧中华消化学会四届委员、全国幽门螺杆菌学组一、二届组长
- ✧中国医促会荣誉常务理事、胃病专业委员会名誉会长
- ✧中国中西医结合学会消化病专业委员会名誉主任委员
- ✧广东中西医结合学会名誉会长、资深专家委员会主任委员
- ✧广东省医学会资深专家委员会常务委员，广东消化学会名誉主委
- ✧《现代消化及介入诊疗》杂志主编、《世界华人消化杂志》副总编

胡伏莲

北京大学第一医院

- 历任：中华医学会 消化分会常委兼秘书；中华医学会 幽门螺杆菌学组组长；北京医学会 消化分会副主委；曾兼任《中华医学杂志》等 10 多种杂志編委或副主编。
- 1986 年分离出幽门螺杆菌。发表论文及述评 270 余篇，分别获《中华医学杂志》创刊 90 周年“金筆奖”和创刊 105 周年“金笔奖”和“金策奖”；其科研成果多次获原卫生部和北京市科技和步奖；北京医学会创立 90 周年 “北京医学会工作突出贡献奖”；主编《幽门螺杆菌感染的基础与临床》;《幽门螺杆菌诊疗指南;《整合胃生态学》等。在国内首先提出“难治性幽门螺杆菌感染” 和“幽门螺杆菌治疗新路径”新理念；2018 年与张声生教授共同组织发布《中西医整合治疗幽门螺杆菌相关“病”-“证”共识》。

张桂英

中南大学湘雅医院

- ✧中南大学湘雅医院内科学教授
- ✧一级主任医师、博士生导师
- ✧中南大学湘雅名医、享受国务院政府特殊津贴专家。
- ✧曾任中南大学湘雅医院内科教研室、诊断学教研室、消化内科主任
- ✧中华消化学会及内科学会委员，湖南省内科学会主任委员
- ✧现任湘雅常德医院消化科主任及学科带头人
- ✧国家精品课程《诊断学》负责人
- ✧中华消化病分会肿瘤协作组委员
- ✧中国医疗保健国际交流促进会消化病分会委员
- ✧湖南省医学会及医师学会常务理事
- ✧湖南省内科专业学会 Hp 学组组长

段丽萍

北京大学第三医院

- ✧教授、主任医师、博士生导师
- ✧北京大学医学部　副主任
- ✧北京大学第三医院消化科　主任医师、教授
- ✧中国女医师协会消化专业委员会　主任委员
- ✧北京医学会肠道微生态与幽门螺杆菌分会　副主任委员
- ✧中国生理学会人体微生态专委会　副主任委员
- ✧中国研究型医院学会神经胃肠病学专业委员会　副主任委员
- ✧中国医师协会专科医学教育委员会副主任委员
- ✧教育部医学教育专家委员会秘书长
- ✧全国医学专业学位研究生教指委秘书长

张声生

北京中医医院

- ✧主任医师，教授，博士生导师，博士后导师
- ✧首都医科大学附属北京中医医院首席专家、消化中心主任、IBD 中心主任
- ✧享受国务院政府特殊津贴专家、国家科技奖励评审专家
- ✧国家中医药局全国脾胃病重点专科协作组组长、脾胃病重点研究室主任
- ✧国家临床重点专科、国家中医脾胃病重点学科带头人
- ✧国家脾胃病区域诊疗中心联盟牵头人
- ✧加拿大多伦多大学医院访问学者

韩英

北京军区总医院

- ✧主任医师、教授、博士生导师
- ✧第二届“国之名医-卓有建树”
- ✧原北京军区总医院原副院长、消化内科主任
- ✧中华医学会消化病学分会专科建设与医学人文协作组组长
- ✧解放军医学会消化病学专业委员会原副主任委员
- ✧中国生命关怀协会远程医学专业委员会副主任委员
- ✧中国医学装备学会消化病分会常委
- ✧《中华消化杂志》《中华健康管理杂志》等编委

唐承薇

华西医院

- ✧中华医学会消化分会候任主委
- ✧中国医师协会消化内科分会副会长
- ✧获得国家杰出青年基金
- ✧全国先进医疗工作者
- ✧全国规划教材《内科学》副主编
- ✧成都市消化专委会主任委员
- ✧华西医院消化内科教授、博导、学科主任

唐旭东

中国中医科学院

- ✧主任医师，博士生导师，首席研究员，岐黄学者
- ✧中国中医科学院　副 院 长
- ✧中药临床疗效与安全性评价国家工程实验室主任
- ✧北京市中医脾胃病研究所　所长
- ✧国家中医药管理局脾虚重点研究室　主任
- ✧中华中医药学会脾胃病分会　主任委员
- ✧中国中西医结合学会　副 会 长河南省医学会消化分会主任委员
- ✧河南省医学会消化内镜分会主任委员

吕有勇

北京大学肿瘤医院

- ✧北京大学肿瘤医院二级教授、北京市肿瘤防治研究所资深研究员、博士生导师
- ✧国家杰出青年基金获得者，美国中华医学会杰出教授奖获得者
- ✧国务院特殊津贴专家
- ✧曾担任北京肿瘤分子生物学高技术实验室主任、首席专家；北京自然科学基金委员会委员和北京基因诊断实验室主任；先后担任北京环境诱变剂学会副理事长，理事长；《WJG》副主编，国际病理学(Journal of pathology)杂志编委,香港中文大学客座（荣誉）教授。国家重大基础研究规划(973)健康科学和中医药专项咨询组专家;

房殿春

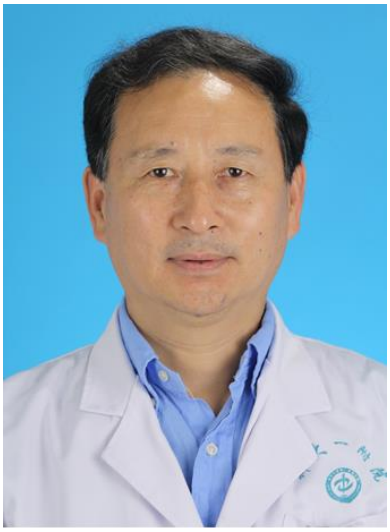
第三军医大学西南医院

- ✧第三军医大学西南医院消化内科教授、主任医师、博士导师
- ✧中华医学会消化病学分会常委、中华医学会消化内镜分会顾问
- ✧中国医师协会消化医师分会常委、中国医促会胃病专委会副会长
- ✧重庆市医学会理事、重庆市消化病专委会名誉主任委员等学术职务
- ✧担任《中华消化杂志》、《中华消化内镜杂志》、《中华胰腺病杂志》、《J Digestive disease》等十余种杂志编委或副主编。为国家有突出贡献中青年专家，解放军总后科技银星，重庆市首批学术技术带头人。

袁耀宗

上海交通大学瑞金医院

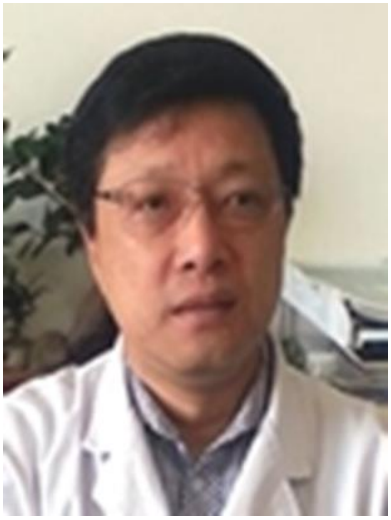
- ✧上海交通大学医学院附属瑞金医院消化科教授、主任医师，博导
- ✧《中华消化杂志》名誉总编辑
- ✧中华医学会消化病学分会委员



李建生

郑州大学第一附属医院

- ✧主任医师、教授、医学博士、博士生导师
- ✧中国医师协会内镜医师分会委员、消化内镜专业委员会委员
- ✧中国医师协会胰腺病专业委员会委员
- ✧《胃肠病学和肝病学杂志》执行主编
- ✧《中华胰腺病杂志》、《临床消化病杂志》、《中国实用内科杂志》等杂志编委
- ✧曾任：
- ✧中华医学会消化病学分会委员
- ✧中国医师协会消化医师分会常委
- ✧河南省医学会消化分会主任委员
- ✧河南省医学会消化内镜分会主任委员



李岩

中国医科大学附属盛京医院

- ✧医学博士，博士生导师，教授、主任医师，内科教研室副主任，消化内科主任
- ✧辽宁省重点学科学术带头人，2003 年开始先后兼任中华医学会消化病分会常委，中国医师协会消化医师分会执行常委
- ✧中国中西医结合学会消化专业委员会常委及消化动力学组组长
- ✧中国国际医疗促进会胃病专业委员会常委，辽宁省医学会及医师协会理事，辽宁省中西医结合学会常务理，辽宁省医学会消化病专业委员会主任委员，辽宁省中西医结合学会消化病专业委员会主任委员，辽宁省医学会肝病专业委员会副主任委员
- ✧《中国实用内科杂志》副主编、顾问，《实用药物与临床》杂志副主编，《中华消化杂志》编委，《世界华人消化杂志》常务编委河南省医学会消化分会主任委员

袁杰力

大连医科大学基础医学院

- ✧大连医科大学基础医学院微生态学教研室 教授
- ✧《中国微生态学杂志》编辑部主任、执行主编
- ✧中华预防医学会微生态学分会 副主任委员
- ✧中国医药教育协会微生态与健康教育专委会 副主任委员
- ✧ 世中联中药（天然药物）发酵研究专业委员会副会长
- ✧中国科技产业促进会微生态医疗专业委员会 副主任委员
- ✧辽宁省微生态学专业委员会 副主任委员
- ✧辽宁省营养学会 常委

王江滨

吉林大学中日联谊医院

- ✧吉林大学中日联谊医院消化内科主任
- ✧医学博士 教授，博士生导师
- ✧中华医学会消化病学会常委
- ✧中国老年医学学会消化分会副会长
- ✧中国免疫学会临床免疫委员会委员
- ✧吉林省消化病学会主任委员
- ✧吉林省肝病学会副主任委员
- ✧国家百千万人才工程专家

盛剑秋

解放军总医院

- ✧解放军总医院第七医学中心消化内科主任
- ✧医学博士、主任医师、教授、博士生导师
- ✧中华医学会消化病分会委员、肿瘤协作组副组长
- ✧中华医学会消化内镜学分会委员、结直肠学组副组长
- ✧全军消化病专业委员会副主任委员
- ✧中国医促会常务理事、消化病学分会副主任委员兼秘书长
- ✧北京医学会消化病学分会副主任委员
- ✧北京医学会消化内镜学分会副主任委员

王化虹

北京大学第一医院

- ✧北京大学第一医院消化内科主任，博导
- ✧中国医师协会消化医师分会常委、中国医师协会循证医学协会常委
- ✧中西医结合学会内镜分会炎症性肠病学组组长
- ✧中华医学会消化病学分会胃肠动力协作组副组长、炎症性肠病组委员
- ✧北京消化病学分会副主委、北京医师协会消化协会副主委
- ✧北京医学会微生态和幽门螺杆菌分会副主委
- ✧中国研究型医院学会中西医整合脾胃消化病专委会副主任委员
- ✧第三届国之名医卓越建树获得者

郑鹏远

郑州大学第五附属医院

- ✧郑州大学第五附属医院 院长、郑州大学康复医学系 系主任
- ✧医学博士、博士生导师、二级教授、主任医师
- ✧郑州大学 Marshall 医学研究中心执行主任、郑州大学医学微生态学及临床营养研究所所长
- ✧享受国务院特殊津贴专家、人事部“百千万人才工程”国家级人选、科技部重点专项（医养结合） 首席专家
- ✧中国康复医学会消化病康复专业委员会 主任委员、中国康复医学会医养结合专业委员会 副主任委员、河南省主动健康和老龄化科技应对研究中心 主任、郑州大学第五附属医院医养结合教研室 主任、中华医学会消化病分会 委员、中华医学会消化专业委员会微生态学组 副组长、中华预防医学会微生态学分会 常委兼消化营养学组组长

郜恒骏

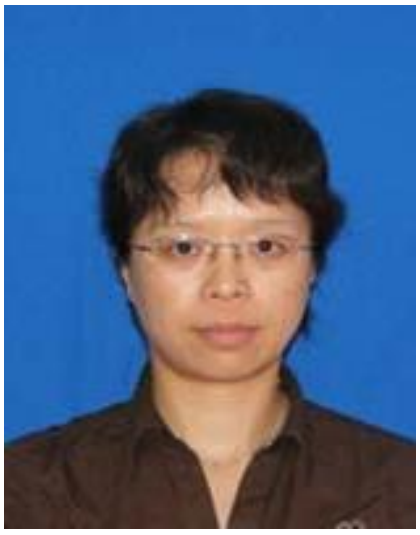
生物芯片上海国家工程研究中心

- ✧同济大学内科学教授、主任医师、博士生导师
- ✧中华医学会消化病学分会委员、生物样本库与转化医学组组长
- ✧同济大学医学院消化疾病研究所所长、Am J Dig Dis 执行主编
- ✧生物芯片上海国家工程研究中心主任、上海分子医学工程技术研究中心主任
- ✧全国生物样本标准化技术委员会主任委员
- ✧中国医药生物技术协会生物样本库分会主任委员
- ✧中国生物样本库联盟主席

张建中

中国疾控中心传染病所

- ✧中国疾控中心传染病所 研究员 副所长
- ✧幽门螺杆菌感染疾病防控 PI
- ✧国家幽门螺杆菌菌株库负责人
- ✧中国生态学会 生态健康与人类生态专业委员会主任委员
- ✧首批新世纪百千万人才工程国家级人选
- ✧中央联系专家



陆红

上海仁济医院

- ✧主任医师，教授，副研究员，博士生导师
- ✧上海市消化疾病研究所副所长
- ✧卫生部消化内科重点实验室副主任
- ✧中华医学会消化病学分会幽门螺杆菌学组组长
- ✧参与研究筛选的根除 Hp 新方案入选中国和欧美 Hp 研究的共识意见和指导方针
- ✧主持 2007 年、2008 年和 2012 年自然科学基金面上项目和 2006 年上海市浦江人才计划，获得 2007 年教育部新世纪优秀人才支持计划和 2007 年上海市卫生系

张国新

江苏省人民医院

- ✧江苏省人民医院消化科　科主任
- ✧江苏省医学会消化分会　候任主委
- ✧江苏省抗癌协会肿瘤内镜专业委员会　主任委员
- ✧江苏省医学会消化分会“Hp 与微生态”学组组长
- ✧中华医学会消化病学分会　委员
- ✧中国医师协会消化内镜分会　常委
- ✧中国抗癌协会肿瘤内镜专业委员会　常委

张振玉

南京市第一医院

✧消化科主任，主任医师，硕士生导师

✧中华医学会 HP 学组委员

✧中华预防医学会微生态分会专业学组成员

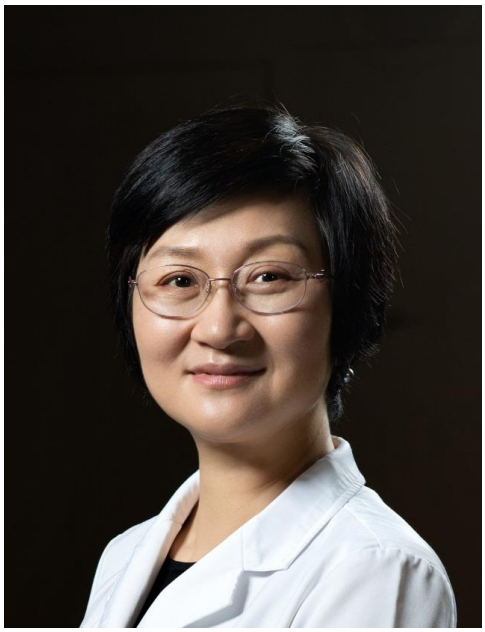
✧江苏省中西医结合消化分会副主任委员

✧南京市消化学会副主任委员

✧江苏省消化内镜常委

✧中国幽门螺杆菌感染与胃癌防控办公室常务理事

✧获得江苏省新技术引进二等奖，氯吡格雷对胃肠道的损伤作用及机制研究获江苏医学科技三等奖，目前重点研究方向幽门螺杆菌及肠道微生态，在省内常规开展 Hp 培养+药敏，达到 Hp 个体化精准治疗。



陈 烨

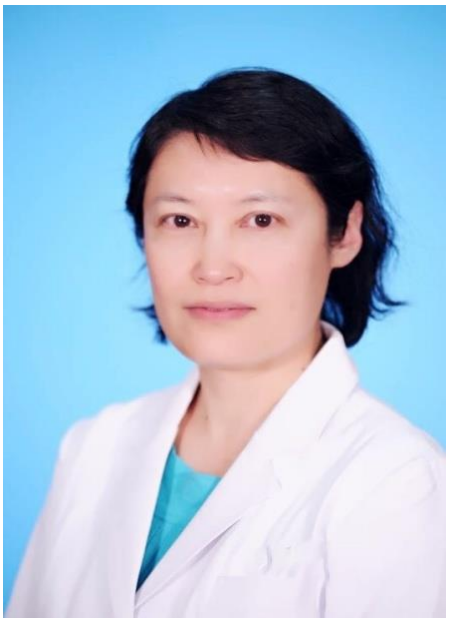
南方医科大学深圳医院

- ✧南方医科大学深圳医院副院长、消化学术带头人、教授、主任医师、博士生/博士后导师
- ✧中华医学会消化病学分会委员、幽门螺杆菌学组副组长、胃肠微生态学组副组长
- ✧中国医师协会消化医师分会委员
- ✧广东省医师协会消化医师分会主任委员
- ✧世界胃肠病学组织(WGO)临床研究委员会委员
- ✧主攻方向：Hp 感染和胃肠微生态失衡相关疾病的临床与转化研究

杜奕奇

海军军医大学长海医院

- ✧海军军医大学长海医院消化内科副主任、主任医师、教授、博导
- ✧中华消化病学会胰腺学组副组长、IBD 学组委员
- ✧中华消化内镜学会小肠镜学组副组长
- ✧中国医师协会胰腺病学专委会常委、总干事



王蔚虹

北京大学第一医院

- ✧北京大学第一医院消化内科教授、主任医师、博士生导师
- ✧中华医学会消化病学分会委员
- ✧中华医学会消化病学分会幽门螺杆菌学组副组长
- ✧中国女医师协会消化专委会副主任委员
- ✧北京医学会消化病学分会常委
- ✧北京医学会肠道微生态与幽门螺杆菌分会副主任委员
- ✧海峡两岸医药卫生交流协会消化病学专委会委员
- ✧中国中西医结合学会消化内镜专业委员会幽门螺杆菌相关疾病专委会副主任委员
- ✧国家药品注册评审专家咨询委员会（消化）委员

刘建湘

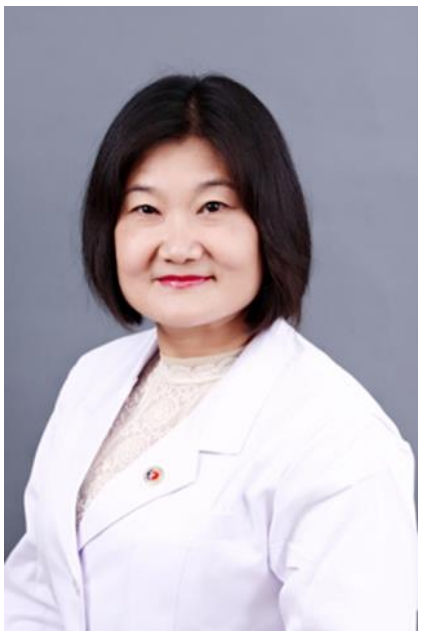
北京大学第一医院

- ✧北京大学第一医院消化内科副主任医师
- ✧内镜中心副主任
- ✧消化内科副主任主持科室工作
- ✧北京医学会动力学组成员
- ✧中华消化心身联盟北京市委员会首届委员
- ✧中国非公立医疗机构协会消化内镜专业委员会第一届委员会常务委员

刘小伟

南大学湘雅医院

- ✧教授、二级主任医师、博士生导师，中南大学湘雅医院消化内科主任
- ✧中国医师协会消化医师分会委员
- ✧中国老年医学会消化病学分会副会长
- ✧中华医学会消化病学分会微生态学组和 IBD 学组委员
- ✧中华医学会消化内镜学分会老年内镜协作组委员
- ✧中华医学会消化病学分会青年协作组副组长
- ✧受湖南省高层次卫生人才“225”工程学科骨干人才和中南大学“531”人才队伍建设工程人才计划支持



姜葵

天津医科大学总医院

- ✧天津医科大学总医院消化科主任医师，教授，博士生导师
- ✧中华医学会消化分会幽门螺杆菌学组委员
- ✧中华医学会消化内镜分会大肠镜学组委员
- ✧中国抗癌协会肿瘤内镜专业委员会委员
- ✧中国医疗保健国际交流促进会中西医结合消化病学分会委员
- ✧天津市中西医结合学会消化专业委员会副主任委员
- ✧天津市医学会消化病学分会幽门螺杆菌学组副组长
- ✧天津市医学会医学人文分会委员\天津市抗癌协会肿瘤营养与支持治疗专业委员会委员

兰春慧

陆军军医大学大坪医院

- ✧陆军军医大学大坪医院消化科 教授 主任医师 博士生导师
- ✧中华医学会消化病分会幽门螺杆菌学组委员
- ✧重庆医学会消化内镜专委会副主任委员
- ✧重庆医学会消化分会幽门螺杆菌学组组长
- ✧长期从事幽门螺杆菌致胃癌的基础和临床研究，主持国家自然科学基金 4 项，以通讯作者在 Am J Gastroenterol 等杂志发表 SCI 论著 18 篇。擅长难治性幽门螺杆菌的个体化治疗、消化道早癌及癌前病变的内镜筛查和诊治

田德安

华中科技大学同济医学院

- ✧华中科技大学同济医学院附属同济医院教授、主任医师、博士生导师
- ✧同济医院消化专科主任
- ✧肝脏胃肠病研究所所长 消化内镜中心主任
- ✧中华医学会消化病学分会常委
- ✧中国医学装备学会消化分会常委
- ✧中国医师协会消化医师分会委员
- ✧中国医师协会消化内镜医师分会委员
- ✧中国医师协会整合医学分会委员
- ✧湖北省消化内镜学会名誉主任委员

杨志平

明品整合医学研究院

✧上海明品整合医学研究院副院长

✧第四军医大学获医学博士，2014-2016 年在清华大学和中国工程院从事博士后研究工作，主要研究方向是整合医学的理论与实践体系。在 Lancet 、Lancet Gastroenterology & Hepatology 等杂志发表 SCI 论文 69 篇，其中第一或通讯作者 20 篇、共同第一作者 17 篇，主译专著 1 部、参编专著 19 部。以项目责任人主持国家自然科学基金 1 项，以项目联系人参与工程院重大咨询研究课题 2 项。

马军

郑州大学第二附属医院

- ✧郑州大学第二附属医院检验科、郑州大学第二附属医院医学研究中心，主任
- ✧郑州大学消化疾病研究所，副所长
- ✧《胃肠病学和肝病学杂志》，编委、编辑部主任
- ✧中国研究型医院学会生物治疗专业委员会常务委员、消化内镜分子影像学专业委员会委员，河南省免疫学会干细胞专业委员会委员；中华医学生物免疫学会常务理事。河南省医院协会会员，河南省医院协会检验管理分会常务委员
- ✧研究方向：干细胞和免疫细胞转化应用；肿瘤防治。

王刚石

解放军总医院

- ✧医学博士，解放军总医院主任医师、教授，博士研究生导师
- ✧解放军总医院第二医学中心消化科副主任
- ✧中华医学会消化病学分会老年消化协作组委员兼秘书
- ✧中华医学会老年医学分会老年消化学组委员
- ✧北京医学会肠道微生态与幽门螺杆菌分会常委
- ✧北京医学会老年医学分会消化与营养学组副组长
- ✧中国老年学与老年医学学会消化病专家委员会常务副主任委员

潘杰

温州市中心医院

- ✧消化内科主任，内镜中心主任，主任医师，内二党支部书记
- ✧温州市医学会消化内镜学分会副主任委员
- ✧浙江省抗癌协会肿瘤内镜专委会副主任委员
- ✧中国幽门螺杆菌感染与胃癌防控办公室常务理事
- ✧温州市重点人群结直肠癌筛查项目办公室主任
- ✧中国抗癌协会肿瘤内镜专业委员会委员
- ✧中国抗癌协会大肠癌专业委员会遗传学组委员
- ✧浙江省医学会消化病学分会 HP 学组副组长

徐美华

中南大学湘雅医院

- ✧医学博士　消化科主任医师　硕士研究生导师
- ✧中南大学湘雅医院内科副主任
- ✧中国幽门螺杆菌信息中心委员
- ✧中华医学会消化分会幽门螺杆菌学组科研协作组成员
- ✧湖南省医学会内科学分会幽门螺杆菌学组副组长
  湖南省中医药及中西医结合学会消化分会副主任委员
- ✧湖南省预防医学会微生态专业委员会委员
- ✧中国中西医结合消化系统专业委员会炎症性肠病专家委员会常务委员，北京医学奖励基金会 IBD 专业委员会委员

王芬

中南大学湘雅三医院

- ✧医学博士，中南大学湘雅三医院主任医师 教授
- ✧博士生导师，消化内科副主任
- ✧湖南省消化专业学会 副主任委员
- ✧中国中西医结合学会消化内镜专委会委员
- ✧中华医学会幽门螺杆菌学组委员
- ✧中华医学会老年消化病协作组委员
- ✧海峡两岸医药交流会消化专委会委员
- ✧北京医学奖励基金会 IBD 专委会委员
- ✧美国消化医师协会国际会员（AGA）
- ✧非可控炎症与肿瘤湖南省重点实验室瘤性病毒和细菌方向 PI

徐灿霞

中南大学湘雅三医院

- ✧教授，博士生导师
- ✧中南大学湘雅三医院消化内科主任医师
- ✧中华医学会湖南分会消化内镜学会副主任委员
- ✧中华医学会消化病学分会第十届幽门螺杆菌学组委员
- ✧中国幽门螺杆菌信息中心学术委员会委员
- ✧中国女医师协会消化专委会委员
- ✧中华医学会湖南分会内科学会幽门螺杆菌学组副组长
- ✧主持国家自然科学基金面上项目 2 项，省部级等课题 10 余项

王学红

中南大学湘雅二医院

- ✧教授 ,医学博士，主任医师，硕士研究生导师
- ✧中南大学湘雅二医院消化内科副主任
- ✧中华医学会消化内镜分会第七届委员会内镜外科学组委员
- ✧湖南省医学会消化内镜分会副主任委员
- ✧湖南省医学会消化分会委员
- ✧吴阶平医学基金会中国炎症性肠病联盟委员
- ✧北京医学奖励基金会炎症性肠病专家委员会委员
- ✧主攻炎症性肠病、消化道早期肿瘤防治等疾病诊治。擅长各种高级内镜诊疗如小肠镜、ESD（内镜下粘膜剥离术）、隧道内镜（如 POEM、STER）等

汪春莲

中南大学湘雅二医院

- ✧中南大学湘雅二医院消化内科教授，主任医师，博士生导师
- ✧湖南省医学会内科学专业委员会第一届幽门螺杆菌学组副组长
- ✧中华消化心身联盟湖南省委员会首届理事
- ✧全国幽门螺杆菌信息中心学术委员
- ✧发表科研论文 20 余篇，参与了五本专著和教材的编写工作，其中 1 部为副主编
- ✧主持 2 项省卫生厅课题；参与 1 项国家自然基金的科研课题和 3 项省级科研课题的研究工作。获得了 2 项湖南医学科学技术进步奖

廖爱军

南华大学附属第一医院

- ✧教授、主任医师、硕士生导师
- ✧湖南省消化专业委员会副主任委员
- ✧湖南省医师协会消化医师分会副会长
- ✧湖南省医学会消化病学分会炎症性肠病协作组副组长
- ✧湖南省早期胃癌防治协作组副组长
- ✧衡阳市消化内镜专业委员会主任委员
- ✧中华消化心身联盟湖南省委员会首届理事
- ✧湖南省中医药和中西医结合学会消化系统疾病专业委员会常务委员
- ✧湖南省消化疾病医疗质量控制中心委员
- ✧湖南省内科学专业委员会 Hp 学组委员
- ✧北京医学奖励基金会炎症性肠病专家委员会委员

廖江涛

湖南省人民医院马王堆院区

- ✧消化内科主任医师，
- ✧现任十病室主任兼消化内科主任
- ✧湖南省消化学会委员
- ✧消化内科学术带头人
- ✧从事消化内科 30 余年
- ✧对消化内科疾病：如胃炎、消化性溃疡、胃肠道肿瘤、肝胆疾病以及疑难杂症的诊治以及内镜的检查、治疗方面有丰富的临床经验

杨铭

永州职业技术学院

- ✧二级教授、一级主任医师、永州职业技术学院副院长
- ✧南华大学/湖南中医药大学硕士生导师
- ✧享受湖南省人民政府特殊津贴专家
- ✧湖南省内科专业委员会副主任委员
- ✧湖南省中西结合消化系病学会副主任委员
- ✧湖南省 HP 学组副组长
- ✧湖南省消化系病专业委员会委员、永州市消化专业委员会主任委员
- ✧公开发表科研论文 45 篇，编写高等学校教材和临床指导性丛书 9（部）本。主持省部级、厅局级课题 11 项,分获市科技进步二等奖 6 项、三等奖 3 项；先后获“永州市十大杰出青年”、“全国卫生系统先进工作者”、“湖南省劳动模范”

宋丰前

娄底市中心医院

- ✧消化内科副主任医师
- ✧娄底市医学会消化内科及消化内镜专业委员会秘书长
- ✧从事消化内科临床工作 10 余年，积累了丰富的临床经验
- ✧主治消化系统疾病、消化内镜检查诊断及内镜下治疗
- ✧多篇论文发表于《中国医师杂志》、《海南医学院学报》等国家级及省级正式期刊

申月明

长沙市中心医院

- ✧消化内科副主任医师，硕士生导师
- ✧湖南省内科专业委员会青年委员
- ✧擅长内科系统常见病、多发病的诊断和治疗

严璐

中南大学湘雅医院

- ✧中南大学湘雅医院消化内科主治医师，医学博士
- ✧湖南省医学会内科学专业委员会青年委员会副主任委员
- ✧湖南省医学会消化病学专业委员会胰腺病学组秘书
- ✧湖南省医学会内科学专业委员会幽门螺杆菌学组秘书
- ✧发表国内外论文 6 篇，其中 SCI 论文 5 篇

成虹

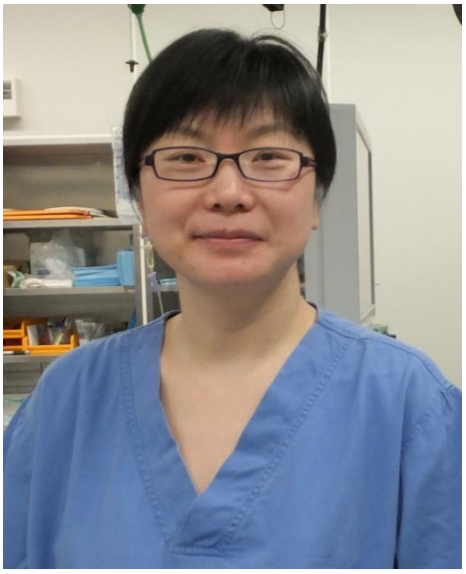
北京大学第一医院

- ✧北京大学第一医院消化内科，主任医师，副教授，研究生导师
- ✧中华医学会消化病学分会第七、八届幽门螺杆菌学组秘书
- ✧中华医学会消化病学分会第九、十届幽门螺杆菌学组副组长
- ✧中国医师协会中西医结合医师分会消化病学专家委员会常委
- ✧中国中医药研究促进会消化整合医学执行理事
- ✧中国医药生物技术协会慢病管理分会委员会常委
- ✧北京医学会肠道微生态及幽门螺杆菌分会常委
- ✧幽门螺杆菌感染与胃癌防控办公室常务理事
- ✧自然基金评审专家、胃肠病学杂志编委
- ✧World Journal Gastroenterology 等杂志审稿专家
- ✧主要从事幽门螺杆菌感染检测、治疗、耐药研究

董欣红

北京大学第一医院

- ✧北京大学第一医院消化科 副主任医师
- ✧北京医学会微生态与幽门螺杆菌学会委员
- ✧中国医疗保健国际交流促进会中西医结合消化病学会委员
- ✧中国医疗保健国际交流促进会中西医结合消化病学分会幽门螺杆菌学组委员
- ✧中国幽门螺杆菌信息中心学术委员会成员



高文

北京大学第一医院

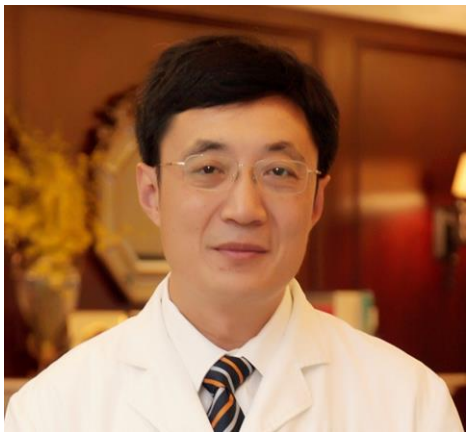
- ✧北京大学第一医院消化科 副主任医师，副教授
- ✧北京医学会幽门螺杆菌与早癌学会委员
- ✧北京医学会微生态与幽门螺杆菌学会委员
- ✧中国医疗保健国际交流促进会中西医结合消化病学会委员
- ✧中国老年学与老年医学学会老年病学分会消化病专家委员会委员
- ✧中国幽门螺杆菌信息中心学术委员会委员，秘书

中国幽门螺杆菌信息中心（www.hpylori.cn）暨大爱高寿网（www.diagoso.net）

杨桂彬

北京大学航天中心医院

- ✧航天中心医院消化科　主任医师
- ✧北京大学航天临床医学院　教授 硕士研究生导师
- ✧北京医学会微生态与幽门螺杆菌分会常委
- ✧北京医学会消化分会六、七、八届委员
- ✧中华医学会消化分会幽门螺杆菌学组　委员
- ✧中国医药生物技术协会慢病管理分会委员
- ✧中国中西医结合学会消化内镜学专业委员会幽门螺杆菌相关疾病专家委员会委员
- ✧中国医疗保健国际交流促进会中西医结合消化病学分会副秘书长



牟方宏

北京大学航天中心医院

- ✧主任医师，硕士研究生导师
- ✧航天中心医院消化科主任医师，内科第二党支部书记
- ✧北京医学会消化分会功能性胃肠病学组委员
- ✧中华消化心身联盟北京委员会委员
- ✧中国幽门螺杆菌信息中心学术委员会成员

冯桂建

北京大学人民医院

- ✧副主任医师，副教授，日本神户大学作访问学者
- ✧北京大学医学部优秀教师
- ✧中华医学会消化内镜分会食管疾病协作组委员
- ✧中华医学会消化分会胃动力学组委员
- ✧中华医学会消化分会功能性胃肠病协作组委员
- ✧中华消化心身联盟北京委员会常委
- ✧中国研究型医院学会妇产科学专业委员会盆底医学研究学组
- ✧北京医学会肠道微生态与幽门螺杆菌感染分会委员
- ✧北京医学会消化分会 Hp 与早癌学组委员

中国幽门螺杆菌信息中心（www.hpylori.cn）暨大爱高寿网（www.diagoso.net）

贾燕

解放军总医院

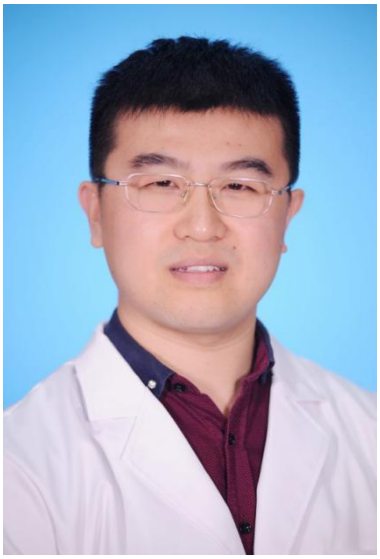
- ✧中国人民解放军总医院第七医学中心消化内科副主任医师
- ✧中国中西医结合学会消化内镜学专业委员会 IBD 专家委员会委员兼秘书
- ✧中国中西医结合学会消化系统疾病专业委员会 IBD 专家委员会委员
- ✧中国医学装备协会消化病学分会 IBD 学组全国委员
- ✧北京医学会肠道微生态与幽门螺杆菌分会第一届委员会委员
- ✧北京医学会消化病学分会肠病学组委员
- ✧北京医学会消化病学分会第九届委员会 Hp 与早癌学组委员
- ✧北京医学奖励基金会 IBD 专家委员会委员
- ✧《中华消化病与影像杂志（电子版）》编委

中国幽门螺杆菌信息中心（www.hpylori.cn）暨大爱高寿网（www.diagoso.net）

刘芳勋

北京大学国际医院

- ✧北京大学国际医院特需国际医疗部
- ✧北京大学国际医院特需国际医疗部主治医师
- ✧北京大学医学部 博士
- ✧北京医学会肠道微生态与幽门螺杆菌分会委员
- ✧中国幽门螺杆菌信息中心编辑委员会组长



滕贵根

北京大学第一医院

✧医学博士，北京大学第一医院消化内科主治医师

✧中国幽门螺杆菌信息中心编委会 副组长

✧中华医学会肠外肠内营养学分会第五届委员会 NUSOC 协作组 委员，中国医疗保健国际交流促进会中西医结合消化病学分会 青年委员，中国中西医结合学会消化内镜学专业委员会 IBD 专家委员会 青年委员

✧专业特长：幽门螺杆菌感染及胃肠微生态相关疾病、炎症性肠病的诊治；主持国家自然科学基金 1 项，北京市自然科学基金 2 项。先后获国家奖学金、北京大学学术创新奖、北京大学年度之星、北京大学医学部天使之星、北京大学第一医院科研希望之星等荣誉

马继征

中医科学院广安门医院

- ✧医学博士
- ✧中国中医科学院广安门医院主治医师
- ✧中国民族医药学会脾胃病分会常务理事
- ✧世界中医药学会联合会消化专业委员会委员
- ✧中国医学保健促进会中西医结合消化病分会青年委员
- ✧中国幽门螺杆菌信息中心编委
- ✧中国健康促进基金会“难治性幽门螺杆菌感染多中心基础与临床研究”专家组成员

董锦沛

北京大学第一医院

✧博士 主治医师 毕业于北京大学医学部

✧中国幽门螺杆菌信息中心 委员

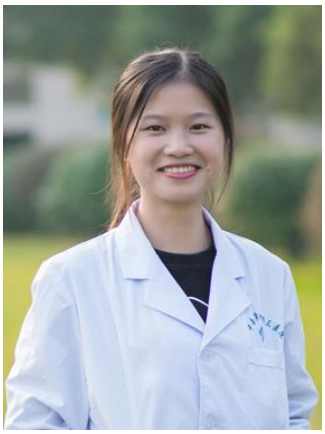
✧在 Am J Gastroenterol 等杂志以第一作者身份发表 SCI 论文 6 篇，累积影响因子 21.97。

✧主持校级课题 1 项，院级课题 1 项

伍丽

湘雅常德医院

- ✧湘雅常德医院消化内科主治医师、医学硕士
- ✧第三届、第四届、第五届湖南幽门螺杆菌相关疾病及消化疾病诊治论坛会议联系人
- ✧主攻方向为消化道早癌诊治、幽门螺旋杆菌相关疾病、自身免疫性肝病、炎症性肠病



袁玲芝

中南大学湘雅三医院

- 中南大学湘雅三医院 2018 级博士研究生，导师王芬教授
- 中南大学 2019-2020 学年优秀学生

王烁

湘雅常德医院

✧湘雅常德医院 医师

✧ 2021 年毕业于中南大学湘雅医学院，获硕士学位

✧ 以第一作者发表 4 篇核心期刊论文

罗举

中南大学湘雅三医院

- ✧中南大学湘雅三医院，主治医师，博士研究生（在读）
- ✧导师是中南大学湘雅三医院消化内科徐灿霞教授
- ✧从事心血管内科，老年医学，消化内科的临床医疗，教学及科研工作多年，具

周晶晶

中南大学湘雅三医院

- ✧中南大学湘雅三医院 2017 级硕士研究生
- ✧导师王芬教授
- ✧长沙市第四医院住院医师
- ✧科研主攻幽门螺旋杆菌治疗
- ✧发表 SCI 论文 1 篇

吴聃

湖南省人民医院

✧湖南省人民医院消化内科在读研究生

✧导师廖江涛教授

赵文芳

中南大学湘雅三医院

✧中南大学湘雅医学院，2014 级临床医学（八年制）在读学生

✧导师是中南大学湘雅三医院消化内科徐灿霞教授

屈鹏

中南大学湘雅三医院

✧中南大学湘雅三医院消化内科
学术型研究生

✧导师 徐灿霞教授

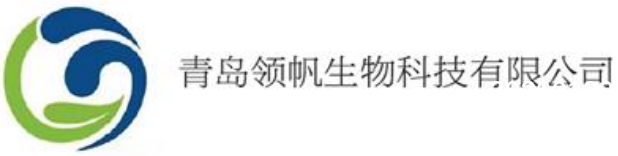
董昀凡

南京市第一医院

✧南京市第一医院消化科 硕士研究生

特别鸣谢


CMS
康哲药业
CHINA MEDICAL SYSTEM


青岛领帆生物科技有限公司


JUMPCAN
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