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· 论著 ·

合生元补充三联疗法根除幽门螺杆菌疗效的 Meta 分析

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[摘要]**目的**:探讨在三联疗法基础上补充合生元对幽门螺杆菌(Hp)根除的效果。**方法**:计算机检索中国知网、万方数据、维普、EMBase、PubMed 和 the Cochrane Library 等数据库,搜集合生元补充三联疗法治疗 Hp 感染的随机对照试验。检索时间从建库到 2020 年 3 月。完成文献筛选、质量评价和提取数据,采用 RevMan 5.3 软件进行 Meta 分析。**结果**:共纳入 4 篇文献,354 例患者。Meta 分析结果显示,补充合生元可提高 Hp 根除率[OR=2.63,95% CI(1.57,4.40),$P<0.01$];进一步分为成人和儿童两个亚组分析,结果显示儿童组[OR=2.38,95% CI(1.32,4.26),$P<0.01$]、成人组[OR=3.68,95% CI(1.22,11.15),$P<0.05$] 补充合生元均可提高 Hp 根除率。**结论**:合生元作为三联疗法的辅助手段,可以提高 Hp 的根除率。但本研究样本量较小,结论需大规模高质量研究加以验证。

[关键词]微生态制剂;合生元;幽门螺杆菌;Meta 分析
[中图分类号]R725.1 [文献标识码]A [文章编号]1672-108X(2022)12-0025-05

Meta-Analysis on Efficacy of Triple Therapy Combined with Synbiotics in Eradication of *Helicobacter Pylori*

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[**Abstract**]**Objective**: To investigate the effects of triple therapy combined with synbiotics in eradication of *Helicobacter pylori* (Hp). **Methods**: CNKI, Wanfang, VIP, EMBase, PubMed and the Cochrane Library were retrieved to collect the randomized controlled trial of triple therapy combined with synbiotics in the treatment of Hp. The retrieval time was from the establishment of the database to Mar. 2020. After literature screening, quality evaluation and data extraction, Meta-analysis was performed by using RevMan 5.3 software. **Results**: A total of 4 studies were enrolled, including 354 patients. Meta-analysis showed that synbiotics supplementation could improve eradication rate of Hp (OR=2.63, 95%CI from 1.57 to 4.40, $P<0.01$). Analysis was further performed by dividing patients into two

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subgroups of adults and children by age, which showed that the eradication rate of Hp could be improved both in children group (OR = 2.38, 95% CI from 1.32 to 4.26, $P<0.01$) and adult group (OR = 3.68, 95% CI from 1.22 to 11.15, $P<0.05$) by synbiotics supplementation. **Conclusion**: Synbiotics, as the adjunct treatment for triple therapy, can improve the eradication rate of Hp. However, the sample size of the study was small, the conclusions need to be verified by large-scale high-quality studies.

[**Keywords**] microecological preparations; synbiotics; *Helicobacter pylori*; Meta-analysis

幽门螺杆菌(*Helicobacter pylori*, Hp)感染是常见的细菌感染,全世界约 50%的人口感染了 Hp,并且将来可能会继续增加[1]。Hp 一旦成功定植在胃中,自发清除相对较少,会发展为持续性慢性感染[2]。尽管大多数宿主无临床症状,但可发展为消化性溃疡、慢性胃炎等疾病,且 1%~3%宿主有胃癌风险[3]。Hp 感染易在儿童期获得,长期感染有致癌风险[4]。在儿童期根除 Hp 不仅对治愈消化系统疾病很重要,还对预防晚期并发症如胃癌具有重要临床意义[5]。有研究[6]表明,在各个年龄段根除 Hp 都可以减少胃癌发生率。共识建议所有 Hp 感染者都应根除感染[7]。三联疗法过去被认为是根除 Hp 最有效的疗法[8],但耐药菌株的发展和抗生素治疗不良反应的发生导致依从性下降,标准三联疗法的 Hp 根除率持续下降至 80%以下,已不再满足临床需求[9-10]。为提高 Hp 根除率,人们已经尝试了多种治疗方案。微生态制剂补充疗法是治疗 Hp 感染的新兴疗法,可以提高 Hp 根除率[11]。合生元是益生菌和益生元的混合制剂,功能显出"1+1>2"的特性[12]。本研究采用 Meta 分析方法系统评价补充合生元的三联疗法对 Hp 根除的疗效,为临床治疗提供参考。

1　资料与方法

1.1　纳入标准和排除标准

1.1.1　*研究对象*　经组织病理学检查、^{13}C 呼气试验(^{13}C-urea breath test, ^{13}C-UBT)、^{14}C-UBT、粪便 Hp 抗原检测(Hp stool antigen test, HpSA)、快速尿素酶试验(rapid urease test, RUT)等一项或多项检查确诊为 Hp 感染。

1.1.2　*干预措施*　试验组为合生元补充三联疗法,对照组为三联疗法。两组三联疗法相同:2 种抗生素和 1 种质子泵抑制剂。

1.1.3　*结局指标*　Hp 根除成功率:治疗结束后至少 4 周经^{13}C-UBT、^{14}C-UBT 或其他方法确认根除结果。

1.1.4　*研究类型*　随机对照试验(RCT)。

1.1.5　*排除标准*　(1)综述、个案报道、队列研究、不相关研究、回顾性研究;(2)重复发表的文献;(3)无法提取数据的文献。

1.2　检索策略

计算机检索数据库:中国知网、万方数据、维普、the Cochrane Library、EMBase、PubMed,并追踪参考文献。中文检索词"合生元""幽门螺杆菌";英文检索词"synbiotics""synbiotic""*Helicobacter pylori*"。检索时限从建库至 2020 年 3 月。PubMed 检索策略:Search "synbiotics" OR "synbiotic" AND "*Helicobacter pylori*"。

1.3　文献筛选、数据收集和偏倚风险评估

两位作者独立筛选文献,提取数据,分歧通过讨论解决。提取数据:第一作者、发表年份、研究地区、样本量、患者年龄、Hp 感染诊断和复查方法、干预措施、结局指标。使用 Cochrane 干预系统评价手册[13]评价纳入文献的偏倚风险:(1)随机序列生成,分配隐藏;(2)实施和测量偏倚,干预措施和结果评价的盲法;(3)结果资料是否完整;(4)有无选择性报道研究结果;(5)其他来源。

1.4　统计学方法

应用 RevMan 5.3 软件,比值比(OR)为二分类变量效应指标,分为成人和儿童两亚组。若 $I^2<50\%$,选择固定效应模型;若 $I^2\geqslant 50\%$,选择随机效应模型。通过意向治疗原则分析 Hp 根除率。$P<0.05$ 为差异有统计学意义。

2　结果

2.1　纳入研究的基本特征

初检共获得 630 篇文献,经过筛选,最终纳入 4 项研究[14-17],共计 354 例患者。见图 1、图 2、表 1。

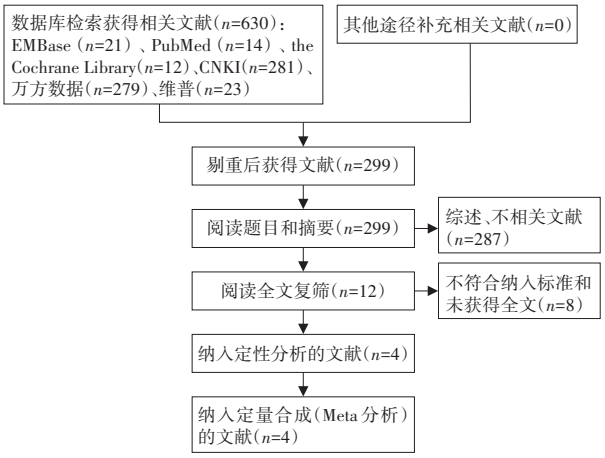

图 1　文献筛选流程

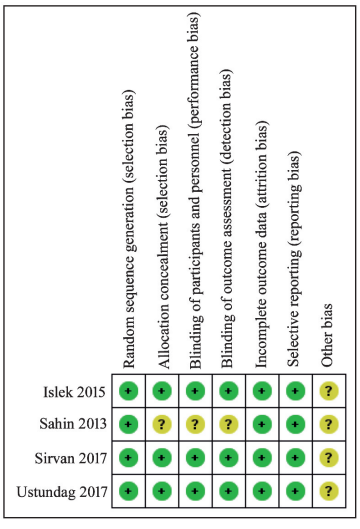

图 2　文献偏倚风险

表 1 纳入研究的基本特征

文献	年份	国家	年龄/岁	例数(T/C)	诊断方法		干预措施		结局指标
					初诊	复查	对照组(C)	试验组(T)	
Sahin O 等[14]	2013	智利	18~85	43/49	组织病理学	^{13}C-UBT	阿莫西林+克拉霉素+奥美拉唑,用法用量不详,2 周	三联疗法;合生元:双歧杆菌+乳酸菌+菊粉,bid,2 周	根除率
Islek A 等[15]	2015	土耳其	5~18	47/46	组织病理学,RUT	^{14}C-UBT	阿莫西林(50 mg/kg,bid)+克拉霉素(15 mg/kg,bid)+兰索拉唑(1 mg/kg,qd),2 周	三联疗法;合生元:双歧杆菌+乳酸菌(5×10^9 CFU/d)+菊粉(900 mg/d),bid,2 周	根除率
Sirvan B N 等[16]	2017	伊朗	5~17	50/50	组织病理学	^{14}C-UBT	阿莫西林(50 mg/kg,bid)+克拉霉素(15 mg/kg,bid)+兰索拉唑(1 mg/kg,qd),2 周	三联疗法;合生元:乳酸菌+菊粉,bid,2 周	根除率
Ustundag G H 等[17]	2017	土耳其	6~16	35/34	组织病理学	^{14}C-UBT	阿莫西林(50 mg/kg,bid)+克拉霉素(15 mg/kg,bid)+奥美拉唑(1 mg/kg,qd),2 周	三联疗法;合生元:双歧杆菌+乳酸菌(5×10^9 CFU/d)+菊粉(900 mg/d),bid,2 周	根除率

2.2 Meta 分析

固定效应模型 Meta 分析显示,试验组和对照组 Hp 根除率分别为 84.00% 和 67.04%,补充合生元可提高 Hp 根除率[OR = 2.63,95% CI(1.57,4.40),$P<0.01$];进一步分为成人和儿童两个亚组分析,结果显示儿童组[OR = 2.38,95% CI(1.32,4.26),$P<0.01$]、成人组[OR = 3.68,95% CI(1.22,11.15),$P<0.05$]补充合生元均可提高 Hp 根除率。见图 3、图 4。

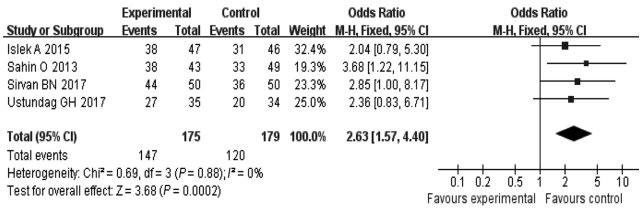

图 3 Hp 根除率的 Meta 分析

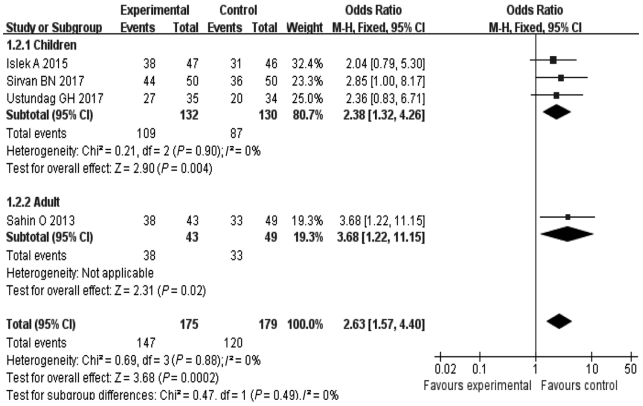

图 4 亚组分析

3 讨论

微生态制剂补充疗法是根除 Hp 的新兴疗法,包括益生菌、益生元和合生元,疗效尚存在争议[16-19]。但 2018 年一项 Meta 分析显示[20],补充乳酸杆菌组的 Hp 根除率增加了约 13%;2020 年梅昭均等[11] Meta 分析显示,补充布拉酵母菌组的 Hp 根除率增加了约 11%;本研究显示,补充合生元组的 Hp 根除率增加了约 17%。考虑儿童和成人的临床异质性,本研究分成人和儿童两组进行亚组分析,结果显示无论成人还是儿童补充合生元均可提高 Hp 根除率。

益生菌根除 Hp 的机制:(1)抑制 Hp 定植。如布拉酵母菌体表面积大,可附着在病原菌上,影响胃黏膜 Hp 定植,有利于 Hp 排泄[21]。布拉酵母菌还可通过合成和释放神经氨酸酶,分解上皮细胞表面的唾液酸,防止 Hp 黏附在胃十二指肠上[22]。嗜酸乳杆菌对胃酸具有良好的耐受性,能够附着在胃黏膜表面,可能影响 Hp 定植[23]。罗伊乳杆菌可产生唾液酸神经节苷脂,干扰 Hp 与上皮细胞受体之间的粘连,抑制 Hp 与胃黏膜的黏附[24]。黏蛋白是保护胃上皮的高分子量糖蛋白,可限制环境物质进入上皮细胞,保护细胞免受病原体侵害[25]。Hp 抑制黏蛋白基因表达,导致胃表面黏蛋白减少[26]。体外研究[27-28]表明,植物乳杆菌和鼠李糖乳杆菌可诱导黏蛋白基因表达,促进细胞外分泌黏蛋白以阻止肠道致病菌的黏附。(2)产生抑菌或抗菌物质。益生菌可分泌乳酸、短链脂肪酸等物质,抑制 Hp 尿素酶活性,抑制 Hp 生长[29]。乳酸还可改变 Hp 形态,使 Hp 失活而发挥杀菌作用[30]。某些乳杆菌属产生细菌素和过氧化氢等直接抑杀 Hp[31]。罗伊乳杆菌分泌罗氏菌素抑制 Hp[31]。此外,某些双歧杆菌可产生拮抗 Hp 的耐热性化合物[32]。(3)抑制 Hp 感染后炎症反应。唾液乳杆菌可抑制 Hp 感染的胃上皮细胞分泌 IL-8,从而减轻 Hp 诱导的炎症[33]。(4)提高治疗依从性。益生菌降低抗生素相关不良事件发生率,增强患者治疗依从性间接地提高了 Hp 根除率[11,34]。合生元是益生菌和益生元的混合制剂,同时发挥益生菌和益生元的功能。合生元拮抗 Hp 的机制与益生菌相似,还可以改善 Hp 感染引起的胃黏膜氧化损伤[35]。

本研究对微生态制剂补充三联疗法根除 Hp 的疗效进行 Meta 分析,表明合生元补充三联疗法可以提高 Hp 根除率,对临床具有较高指导意义,但仍存在一定局限性:样本量较小,无法对不同菌株、剂量等因素进行亚组分析以检测其对结果的影响。因此,本研究结论还需开展大规模高质量研究加以验证。

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· 论著 ·

肠道菌群及其代谢产物在过敏性哮喘患儿中的作用

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[摘要]**目的**:探讨常见肠道菌群及其代谢产物在过敏性哮喘(AA)患儿病情进展中的作用。**方法**:选取 2019-2021 年我院门急诊及住院收治的 80 例 AA 急性发作期患儿作为研究对象,参照《儿科学(第 9 版)》中 AA 急性发作期病情严重程度分级将患儿分为轻度组、中度组与重度组,比较不同病情严重程度 AA 急性发作期患儿的基线资料、常见肠道菌群及其代谢产物,重点分析常见肠道菌群及其代谢产物与 AA 急性发作期患儿病情严重程度的关系。**结果**:80 例 AA 急性发作期患儿中轻度 28 例、中度 34 例、重度 18 例;轻度组患儿乳酸杆菌、双歧杆菌、乙酸、丁酸水平最高,其次为中度组,重度组最低,差异有统计学意义($P<0.05$);重度组患儿大肠埃希菌、脂多糖水平最高,其次为中度组,轻度组最低,差异有统计学意义($P<0.05$);经 Kendall's tau-b 相关性检验显示,AA 急性发作期患儿病情严重程度分级与乳酸杆菌、双歧杆菌、短链脂肪酸的乙酸与丁酸水平呈负相关($r<0$, $P<0.05$),与大肠埃希菌、脂多糖水平呈正相关($r>0$, $P<0.05$);经有序回归分析显示,乳酸杆菌、双歧杆菌、乙酸、丁酸水平高是 AA 病情程度分级的保护因素($OR<1$, $P<0.05$),大肠埃希菌、脂多糖水平高是其危险因素($OR>1$, $P<0.05$);绘制决策曲线结果显示,在高风险阈值 0~1.0 范围内乳酸杆菌、双歧杆菌、大肠埃希菌联合评估 AA 急性发作期患儿病情程度分级的净收益率均>0,乙酸、丁酸、脂多糖联合评估 AA 急性发作期患儿病情程度分级的净收益率均>0,有临床意义。**结论**:常见肠道菌群中乳酸杆菌、双歧杆菌、大肠埃希菌及其代谢产物乙酸、丁酸、脂多糖与 AA 急性发作期患儿病情严重程度有关,可能在 AA 的病情进展中发挥一定作用。

[关键词]过敏性哮喘;儿童;肠道菌群;代谢产物
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Effects of Intestinal Flora and Its Metabolites in Children with Allergic Asthma

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[**Abstract**]**Objective**: To explore the effects of common intestinal flora and its metabolites in the progression of allergic asthma (AA) in children. **Methods**: Eighty children with acute attack of AA admitted into outpatient, emergency and inpatient departments of the hospital from 2019 to 2021 were selected as the research subjects. All children were divided into the mild group, moderate group and severe group, according to the grading of acute attack of AA condition in *Pediatrics* (9^{th} *Edition*). The baseline data, common intestinal flora and its metabolites of acute attack of AA in children with different disease degrees were compared. Correlation between common intestinal flora and its metabolites and the severity of children with acute attack of AA was emphatically analyzed. **Results**: Among 80 children with acute attack of AA, 28 cases were mild, 34 cases were moderate and 18 cases were severe. The levels of *Lactobacillus*, *Bifidobacterium*, acetic acid and butyric acid were the highest in the mild group, followed by the moderate group and the severe group, with statistically significant differences ($P<0.05$). The levels of *Escherichia coli* and lipopolysaccharide were the highest in the severe group, followed by the moderate group and the mild group, with statistically significant differences ($P<0.05$). Results of Kendall's tau-b correlation test showed that the grade of acute attack of AA was negatively correlated with the levels of *Lactobacillus*, *Bifidobacterium*, acetic acid and butyric acid of short-chain fatty acids ($r<0$, $P<0.05$), and positively correlated with the levels of *E. coli* and lipopolysaccharide ($r>0$, $P<0.05$). Results of ordered regression analysis showed that the high levels of *Lactobacillus*, *Bifidobacterium*, acetic acid and butyric acid were the protective factors for the grading of AA ($OR<1$, $P<0.05$), and the high levels of *Escherichia coli* and lipopolysaccharide were the risk factors ($OR>1$, $P<0.05$). Results of decision curve showed that the net benefit rate of joint

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