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· 论著 ·

益生菌预防低出生体质量儿坏死性小肠结肠炎效果的 Meta 分析

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[摘要]**目的**:比较不同益生菌和安慰剂预防低出生体质量儿坏死性小肠结肠炎(NEC)的效果,初步确定推荐预防方案。**方法**:检索中国知网、万方、维普、PubMed、Web of Science、the Cochrane Library、OVID、Medline、EMBase 等数据库,筛选出建库至 2022 年 7 月 31 日发表的益生菌和安慰剂预防 NEC 相关的随机对照试验(RCT)。采用 Cochrane 协作网偏倚风险评估工具评估 RCT 质量,RevMan 5.3 软件进行 Meta 分析。**结果**:纳入 43 项 RCT,共有 10 247 例低出生体质量儿。Meta 分析结果显示,与安慰剂组相比,益生菌组 NEC 发生率[OR=0.55,95%CI(0.46,0.66)]、病死率[OR=0.66,95%CI(0.56,0.79)]均降低(P 均<0.01)。亚组分析结果显示,与安慰剂组相比,益生菌混合制剂组 NEC 发生率[OR=0.41,95%CI(0.29,0.57)]、病死率[OR=0.51,95%CI(0.40,0.66)]降低(P 均<0.01),且降低幅度大于益生菌单一制剂组。**结论**:益生菌预防性应用可降低低出生体质量儿 NEC 的发生率和病死率,且混合制剂效果优于单一制剂,推荐在益生菌预防 NEC 方案中采用混合制剂。

[关键词]坏死性小肠结肠炎;益生菌;低出生体质量儿;随机对照试验
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Meta-Analysis on Efficacy of Probiotics in the Prevention of Necrotizing Enterocolitis in Infants with Low Birth Weight

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[**Abstract**] **Objective**: To compare the efficacy of different probiotics and placebo in the prevention of necrotizing enterocolitis (NEC) in infants with low birth weight, so as to preliminary formulate recommendations for prevention. **Methods**: CNKI, Wanfang, VIP, PubMed, Web of Science, the Cochrane Library, OVID, Medline, EMBase databases were retrieved to collect the randomized controlled trials (RCT) of probiotics and placebo in the prevention of NEC. The retrieval time was from the establishment of the database to Jul. 31st, 2022. The quality of the included RCT was evaluated by the risk of bias assessment tool of Cochrane Collaboration Network. Meta-analysis was carried out by using RevMan 5.3 software. **Results**: There were 43 RCT, including 10,247 infants with low birth weight. Compared with placebo group, the incidence of NEC (OR=0.55, 95%CI from 0.46 to 0.66) and mortality (OR=0.66, 95%CI from 0.56 to 0.79) in the probiotics group decreased (P<0.01). According to subgroup analysis, compared with placebo group, the incidence of NEC (OR=0.41, 95%CI from 0.29 to 0.57) and mortality (OR=0.51, 95%CI from 0.40 to 0.66) in the probiotics combination group decreased (P<0.01), and the reduction was greater than that in the single probiotics group. **Conclusion**: Prophylactic use of probiotics can reduce the incidence and mortality of NEC in infants with low birth weight, and the effect of mixed preparation is better than that of single preparation, it is recommended to use mixed preparation in probiotics in the prevention of NEC.

[**Keywords**] necrotizing enterocolitis; probiotics; infants with low birth weight; randomized controlled trial

坏死性小肠结肠炎(necrotizing enterocolitis,NEC)是一种多发且严重的肠道炎性疾病,>90%出现在新生儿[1],是新生儿死亡原因之一,病死率达 30%~50%[2]。虽然许多研究已经证明益生菌预防 NEC 有效,但是由于益生菌的功能具有物种特异性[3],研究忽略了不同益生菌属作用的差异,目前仍没有统一的预防 NEC 的益生菌方案。为此,本研究通过 Meta 分析对不同益生菌制剂的预防效果进行评估,为临床采用益生菌预防 NEC 提供参考。

1 资料与方法

1.1 文献检索策略

检索中国知网、万方、维普、PubMed、Web of Science、the Cochrane Library、OVID、Medline、EMBase 等数据库。中文检索词:"新生儿坏死性小肠结肠炎""双歧杆菌""芽孢杆菌""乳杆菌""酵母菌""益生菌""低出生体质量儿"等;英文检索词:"necrotizing enterocolitis""*Lactobacillus*""*Bifidobacterium*""*Bacillus*""*Saccharomyces*""probiotics""low birth weight infants"等。采用主题与自由途径结合的方式进行检索,同时手工检索纳入文献的参考文献,检索时限从建库至 2022 年 7 月 31 日。

1.2 文献纳入标准与排除标准

纳入标准:(1)出生体质量<2 500 g 的新生儿,包括足月儿和早产儿;(2)在胃肠减压、抗生素等常规治疗的基础上,干预组加用乳杆菌属、双歧杆菌属、芽孢杆菌属、酵母属或益生菌混合制剂,从入院开始到出院结束,对照组给予安慰剂;(3)结局指标为 NEC(根据 Bell 标准

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进行诊断和分级）发生率和（或）病死率[3]；（4）随机对照试验（RCT）。排除标准：（1）结局指标与本研究设计不符；（2）动植物实验或体外试验；（3）先天性缺陷（如先天性胆道闭锁症、先天性心脏病等）或母婴相关疾病（如先天性梅毒、艾滋病等）；（4）重复文献。

1.3　数据提取及文献质量评价

文献数据提取内容分为 8 个方面：干预时间、患者特征、样本量、作者姓名、益生菌种类、益生菌剂量、结局指标和发表年份。数据由 2 个研究者独立收集，采用 Cochrane 协作网偏倚风险评估工具进行质量评估；如果产生不同意见，由研究的主持人评估解决。

1.4　统计学方法

采用 RevMan 5.3 软件进行 Meta 分析。计数资料以优势比（OR）及其 95% CI 表示，$P<0.05$ 为差异有统计学意义。$P\geq0.1$、$I^2<50\%$ 表示各研究无异质性，采用固定效应模型；$P<0.1$、$I^2\geq50\%$ 表示各研究存在异质性，采用随机效应模型。采用漏斗图评估发表偏倚。

2　结果

2.1　文献检索与质量评价

初检选出文献 1 862 篇，通过 EndNote X7 软件及人工筛检后，最终纳入 RCT 文献 43 篇[4-46]，共 10 247 例低出生体质量儿，大部分 RCT 均严格遵循盲法，涉及 5 种益生菌制剂：乳杆菌属、双歧杆菌属、芽孢杆菌属、酵母属、益生菌混合制剂。文献筛选流程见图 1，质量评估见图 2，纳入研究基本情况见表 1。

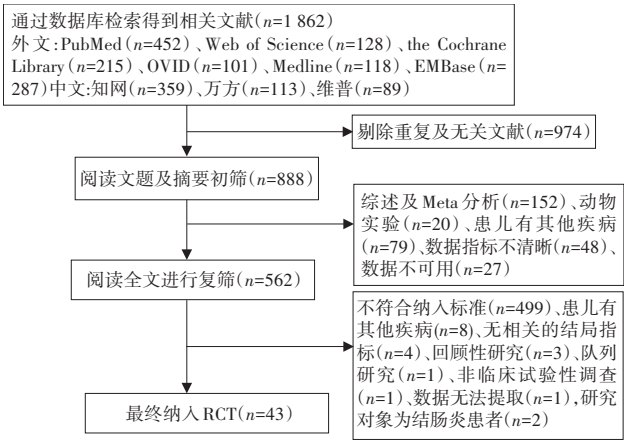
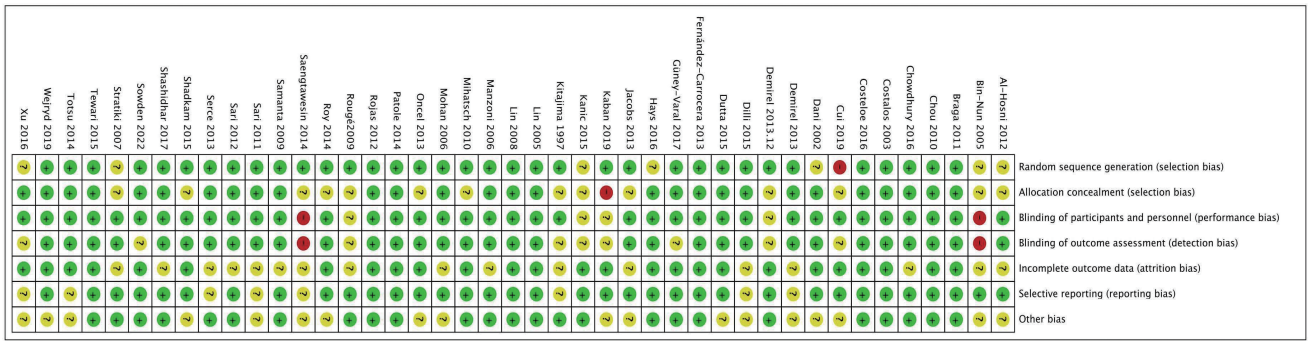


图 1　文献筛选流程



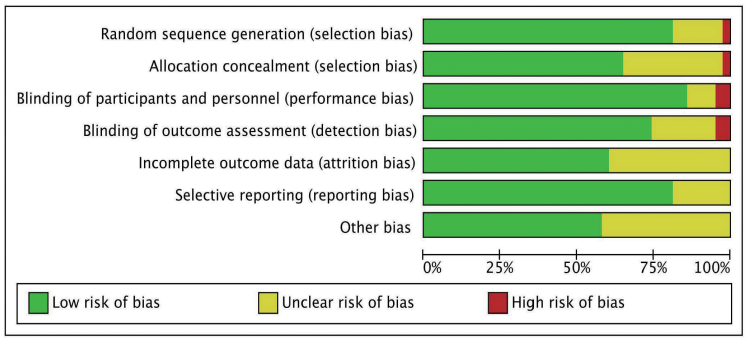


图 2　研究质量评估

2.2　Meta 分析结果

2.2.1　NEC 发生率　43 篇文献均记录了 NEC 发生率。益生菌组 NEC 发生率为 3.59%，安慰剂组为 6.32%。Meta 分析结果显示，益生菌组 NEC 发生率降低［OR = 0.55，95% CI（0.46，0.66），$P<0.01$］，无异质性（$I^2=13\%$，$P=0.23$）。益生菌亚组分析显示：与安慰剂组相比，益生菌混合制剂组［OR = 0.41，95% CI（0.29，0.57），$P<0.01$］，无异质性（$I^2=10\%$，$P=0.33$）；乳杆菌属组［OR = 0.50，95% CI（0.34，0.73），$P<0.01$］，无异质性（$I^2=0$，$P=0.68$）；双歧杆菌属组［OR = 0.71，95% CI（0.51，0.97），$P<0.05$］，无异质性（$I^2=49\%$，$P=0.07$）；芽孢杆菌属组和酵母属组比较差异均无统计学意义。出生体质量亚组分析显示：与安慰剂组相比，VLBWI 组［OR = 0.40，95% CI（0.32，0.52），$P<0.01$］，无异质性（$I^2=0$，$P=0.57$）；LBWI 组和 ELBWI 组比较差异均无统计学意义。见图 3、图 4。

表 1 纳入研究基本情况

纳入研究	年份	样本量(T/C)	研究对象	益生菌组干预方案	结局指标
Al-Hosni M 等[4]	2012	50/51	ELBWI	鼠李糖乳杆菌+长双歧杆菌,0.50×10^9 CFU,1 次/日,肠内喂养至出院	①②
Bin-Nun A 等[5]	2005	72/73	VLBWI	婴儿双歧杆菌+嗜热链球菌+双歧杆菌,0.35×10^9 CFU,1 次/日,肠内喂养至出院	①②
Braga T D 等[6]	2011	119/112	VLBWI	短双歧杆菌+干乳酪杆菌,3.50×10^9 CFU,1 次/日,生后 2~30 d	①②
Chou I C 等[7]	2010	153/148	VLBWI	嗜酸乳杆菌+婴儿双歧杆菌,1.00×10^9 CFU,2 次/日,肠内喂养至出院	①②
Chowdhury T 等[8]	2016	52/50	VLBWI	益生菌混合物,6.00×10^9 CFU,第 1 次喂养至出院	①
Fernández-Carrocera L A 等[9]	2013	75/75	VLBWI	嗜酸乳杆菌+鼠李糖乳杆菌+干酪乳杆菌+植物乳杆菌+婴儿双歧杆菌,1 g,1 次/日,肠内喂养至出院	①②
Güney-Varall I 等[10]	2017	70/40	VLBWI	鼠李糖乳杆菌+植物乳杆菌+动物双歧杆菌+干酪乳杆菌,2.50×10^9 CFU,出生至出院	①②
Hays S 等[11]	2016	145/52	VLBWI	乳酸双歧杆菌+长双歧杆菌,1.00×10^9 CFU,1 次/日,生后 7 d 内开始应用 4~6 周	①
Jacobs S E 等[12]	2013	548/551	VLBWI	婴儿双歧杆菌+芽孢杆菌+两歧双歧杆菌,1.00×10^9 CFU,2 次/日,肠内喂养至出院	①②
Kanic Z 等[13]	2015	40/40	VLBWI	嗜酸乳杆菌+粪便大肠杆菌+婴儿双歧杆菌,0.60×10^7 CFU,2 次/日,第 1 次喂养至出院	①②
Lin H C 等[14]	2005	180/187	VLBWI	嗜酸乳杆菌+婴儿双歧杆菌,125 mg/kg,2 次/日,生后 7 d 至出院	①②
Rougé C 等[15]	2009	45/49	VLBWI	长双歧杆菌+鼠李糖乳杆菌,1.00×10^8 CFU,第 1 次喂养至出院	①②
Roy A 等[16]	2014	56/56	VLBWI	嗜酸乳杆菌+长双歧杆菌+双歧杆菌+乳酸双歧杆菌,1 g,1 次/日,生后 3 d 至出院	①②
Samanta M 等[17]	2009	91/95	VLBWI	婴儿双歧杆菌+双歧杆菌+长双歧杆菌+嗜酸乳杆菌,2.50×10^9 CFU,2 次/日,第 1 次喂养至出院	①②
Shashidhar A 等[18]	2017	52/52	VLBWI	嗜酸乳杆菌+鼠李糖乳杆菌+长双歧杆菌+布拉酵母菌,1.25×10^9 CFU,1 次/日,肠内喂养至出院	①②
Sowden M 等[19]	2022	100/100	VLBWI	嗜酸乳杆菌+双歧双歧杆菌+婴儿双歧杆菌,0.67×10^9 CFU,1 次/日,生后 0~28 d	①
Dani C 等[20]	2002	295/290	VLBWI	鼠李糖乳杆菌,6.00×10^9 CFU,1 次/日,第 1 次喂养至出院	①
Manzoni P 等[21]	2006	39/41	VLBWI	鼠李糖乳杆菌,6.00×10^9 CFU,第 1 次喂养开始,持续 6 周	①②
Oncel M Y 等[22]	2013	200/200	VLBWI	罗伊乳杆菌,1.00×10^8 CFU,1 次/日,第 1 次喂养至出院	①②
Rojas M A 等[23]	2012	372/378	LBWI	罗伊乳杆菌,1.00×10^8 CFU,1 次/日,生后 48 h 至出院	①②
Sari F N 等[24]	2012	86/88	VLBWI	产孢乳杆菌,0.35×10^9 CFU,2 次/日,第 1 次喂养至出院	①
Sari F N 等[25]	2011	110/111	VLBWI	产孢乳杆菌,0.35×10^9 CFU,1 次/日,第 1 次喂养至出院	①②
Costeloe K 等[26]	2016	650/660	LBWI	短双歧杆菌,8.80×10^9 CFU,1 次/日,生后至营养状况修正至胎龄 36 周情况	①②
Dilli D 等[27]	2015	100/100	VLBWI	乳酸双歧杆菌,5.00×10^9 CFU,生后 7 d 至出院	①②
Mihatsch W A 等[28]	2010	91/89	VLBWI	乳酸双歧杆菌,2.00×10^9 CFU,1 次/日,肠内喂养至出院	①②
Patole S 等[29]	2014	77/76	VLBWI	短双歧杆菌,3.00×10^9 CFU,1 次/日,肠内喂养至出院	①②
Stratiki Z 等[30]	2007	41/34	LBWI	乳酸双歧杆菌,2.00×10^7 CFU,肠内喂养至出院	①
Mohan C 等[31]	2006	21/17	LBWI	乳酸双歧杆菌,3.48×10^9 CFU,1 次/日,生后 4~20 d	①
Costalos C 等[32]	2003	51/36	LBWI	布拉酵母菌,1.00×10^9 CFU,2 次/日,肠内喂养至第 30 天	①
Demirel G 等[33]	2013	91/90	VLBWI	布拉酵母菌,5.00×10^9 CFU,1 次/日,肠内喂养至出院	①②
Demirel G 等[34]	2013	135/136	VLBWI	布拉酵母菌,5.00×10^9 CFU,1 次/日,第 1 次喂养至出院	①②
Serce O 等[35]	2013	104/104	VLBWI	布拉酵母菌,0.50×10^9 CFU,2 次/日,肠内喂养至出院	①②
Tewari V V 等[36]	2015	123/121	LBWI	克劳芽孢杆菌,0.80×10^9 CFU,3 次/日,生后 1 d 至出院	①②
Lin H C 等[37]	2008	217/217	VLBWI	嗜酸乳杆菌+婴儿双歧杆菌,125 mg/kg,2 次/日,生后 7 d 至出院	①②
Dutta S 等[38]	2015	114/35	VLBWI	嗜酸乳杆菌+鼠李糖乳杆菌+长双歧杆菌+布拉酵母菌,1.00×10^9 CFU,1 次/日,出生至出院	①②
Saengtawesin V 等[39]	2014	31/29	VLBWI	乳杆菌+双歧杆菌,2.00×10^9 CFU,2 次/日,肠内喂养至出院	①
Cui X 等[40]	2019	45/48	VLBWI	罗伊乳杆菌,1.00×10^8 CFU,1 次/日,肠内喂养至出院	①
Kaban R 等[41]	2019	47/47	VLBWI	罗伊乳杆菌,1.00×10^8 CFU,1 次/日,肠内喂养至出院	①②
Shadkam M N 等[42]	2015	30/30	LBWI	罗伊乳杆菌,1.00×10^8 CFU,1 次/日,生后 7 d 内开始至出院	①②
Wejryd E 等[43]	2019	68/66	ELBWI	罗伊乳杆菌,1.25×10^8 CFU,1 次/日,生后 3 d 内开始至出院	①②
Kitajima H 等[44]	1997	45/46	VLBWI	短双歧杆菌,0.50×10^9 CFU,1 次/日,出生 24 h 开始持续 28 d	①
Totsu S 等[45]	2014	153/130	VLBWI	乳酸双歧杆菌,2.50×10^9 CFU,出生 48 h 开始至体质量达 2 000 g	①②
Xu L 等[46]	2016	51/62	LBWI	布拉酵母菌,0.50×10^9 CFU,1 次/日,肠内喂养至出院	①

注:益生菌组(T),采用各种益生菌干预;安慰剂组(C),给予安慰剂;超低出生体质量儿(ELBWI,出生体质量<1 000 g);极低出生体质量儿(VLBWI,出生体质量<1 500 g);低出生体质量儿(LBWI,出生体质量<2 500 g);①NEC 发生率;②病死率

2.2.2 *病死率* 31 篇文献记录了病死率。益生菌组病死率为 5.66%,安慰剂组为 8.22%。Meta 分析结果显示,益生菌组病死率降低[OR=0.66,95% CI(0.56,0.79),$P<0.01$],无异质性($I^2=22\%$,$P=0.14$)。益生菌亚组分析显示:与安慰剂组相比,益生菌混合制剂组[OR=0.51,95% CI(0.40,0.66),$P<0.01$],无异质性($I^2=40\%$,$P=0.05$);其他亚组比较差异均无统计学意义。出生体质量亚组分析显示:与安慰剂组相比,VLBWI 组[OR=0.56,95% CI(0.45,0.70),$P<0.01$],无异质性($I^2=28\%$,$P=0.10$);LBWI 组和 ELBWI 组比较差异均无统计学意义。见图 5、图 6。

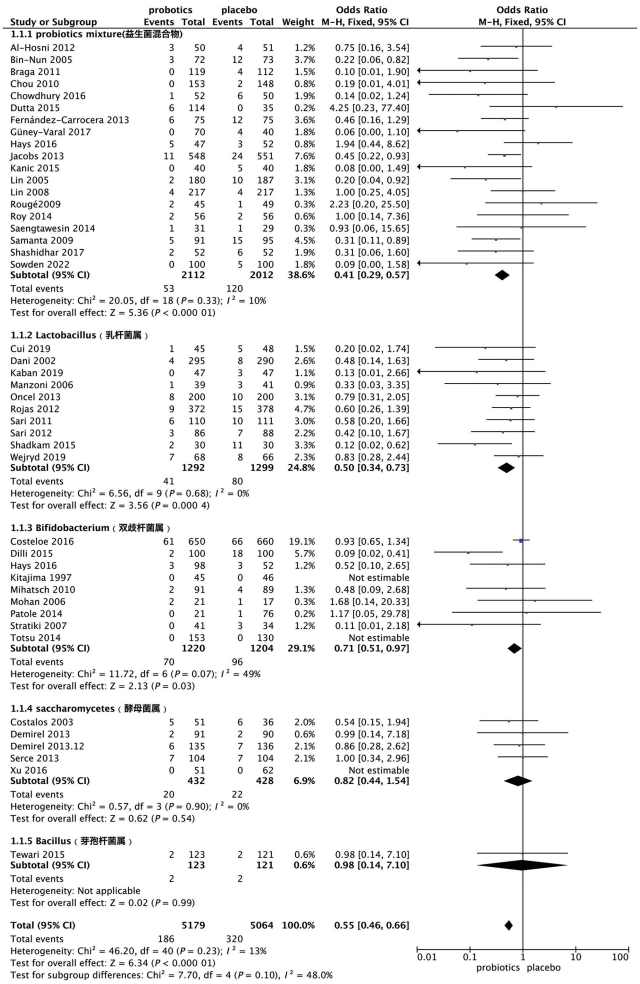


图 3　益生菌与 NEC 发生率的 Meta 分析

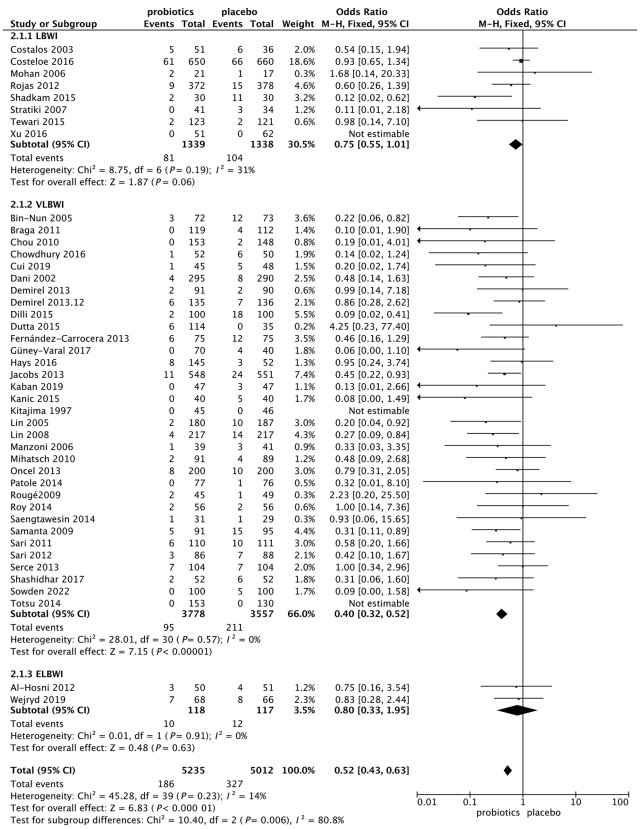


图 4　出生体质量与 NEC 发生率的 Meta 分析

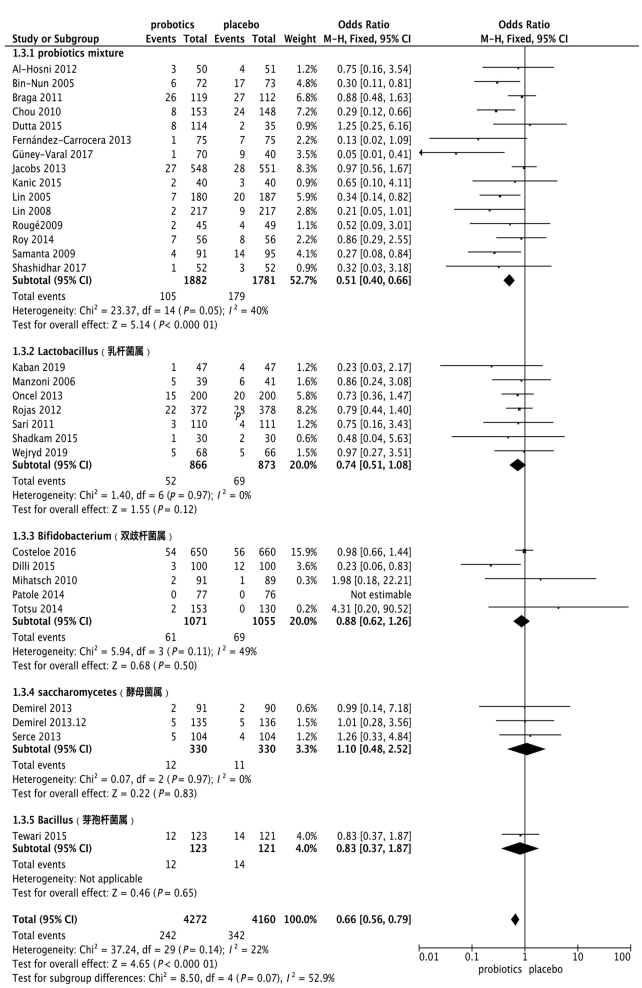


图 5　益生菌与病死率的 Meta 分析

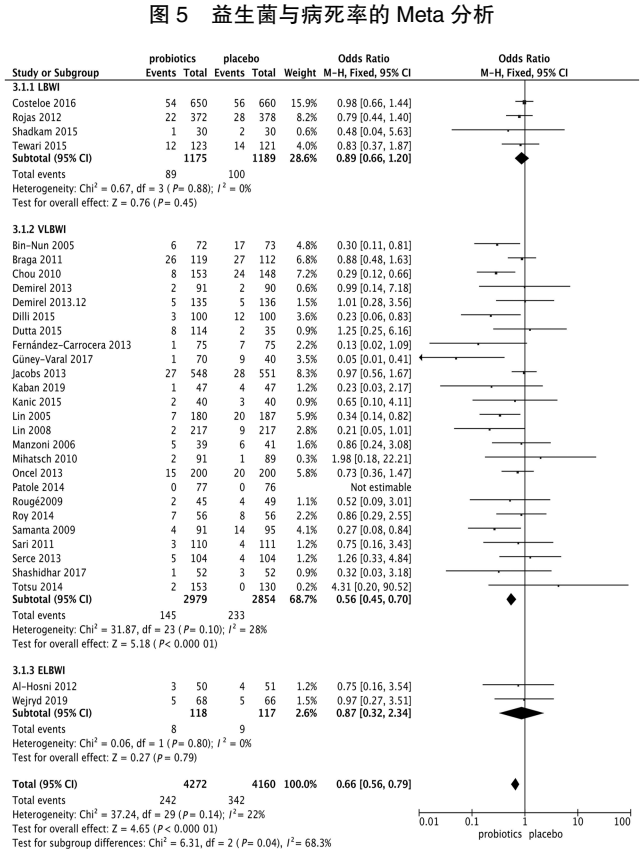


图 6　出生体质量与病死率的 Meta 分析

2.3 发表偏倚

本研究分别以 NEC 发生率(上)、病死率(下)为指标进行发表偏倚评价,绘制漏斗图,结果显示未见明显的发表偏倚,见图 7。

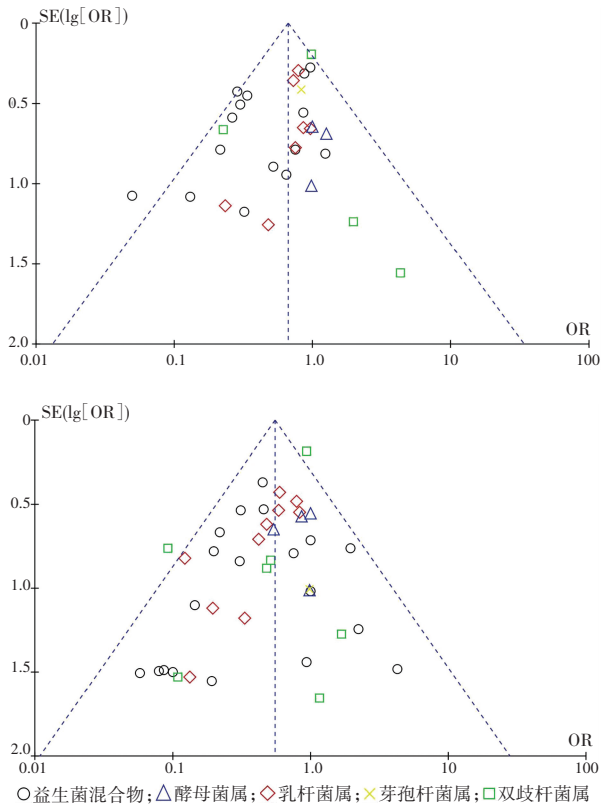


图 7 发表偏倚漏斗图

3 讨论

肠道菌群能促进免疫功能的建立,在人类生长发育中起着重要作用[47-48]。NEC 患儿肠道菌群与健康新生儿相比,多样性低,菌群构成中变形菌门占比增加,拟杆菌门和放线菌门占比较低[49]。NEC 的发病机制尚未明确,众多研究表明与肠道菌群失调引起的相关代谢途径中酶活性改变及代谢产物变化有关[50-52]。Saw H 等[53]表明,肠道菌群失调是 NEC 发生的重要因素。益生菌通常是指对适量摄取的食用者机体产生正面作用的活性微生物[54]。目前市场上常见的益生菌多属于拟杆菌门和放线菌门,其中以双歧杆菌和乳杆菌多见。健康新生儿肠道菌群主要由拟杆菌、双歧杆菌、副细菌等厌氧菌组成,其中占比最大的是双歧杆菌[55]。由此可知,在健康新生儿肠道菌群中,益生菌占主导地位。益生菌作为优势菌群,影响着宿主免疫系统、病原体跨膜迁移及定植、远期生长发育健康等[56]。因此,在研究 NEC 时,益生菌被越来越多的研究者关注,很多儿科医师主张益生菌对预防 NEC 有重要作用,并且益生菌在一定程度上可以降低新生儿的病死率[57]。虽然有很多相关的权威性研究证明益生菌在降低 NEC 发生率及病死率方面有效,但仍没有对不同益生菌属预防 NEC 的作用进行比较,以确定新生儿 NEC 的最佳预防方案。

本研究结果显示,在降低 NEC 发生率和新生儿病死率方面,益生菌具有明显效果。益生菌亚组分析显示:(1)益生菌混合制剂可降低 NEC 发生率及病死率。这可能是因为正常肠道菌群是由多种细菌组成,益生菌混合制剂的组成有着类似多样性,并且不同菌株之间具有协同作用[58],促进了益生菌粘附于新生儿肠壁。(2)乳杆菌属和双歧杆菌属可以降低 NEC 发生率,而未能降低新生儿的病死率。这可能是因为新生儿黏膜屏障及免疫系统尚未完全发育成熟,单一益生菌不易粘附于肠壁,出现异位定植,从而引起感染甚至死亡。(3)单独使用酵母属并不能预防 NEC 的发生及降低病死率。有研究[59]表明,酵母菌属具有协同作用,促进其他益生菌的生存及生长。这可能是单独使用酵母菌属无效的原因。出生体质量亚组分析显示:(1)益生菌能降低 VLBWI 的 NEC 发生率和病死率[60-61]。(2)在 LBWI 和 ELBWI 中,益生菌在降低 NEC 发生率和病死率方面无明显效果,可能与样本量较小有关,也可能与益生菌无法粘附到 ELBWI 的肠壁有关。

本研究的局限性:(1)纳入文献未对益生菌的安全性进行评价,也未区分安全剂量和有效剂量;(2)本研究数据有局限性,未能在每个益生菌属中根据不同出生体质量对患儿进行亚组分析,还有待进一步研究;(3)文献只是对近期效果的观察。

综上所述,对于预防低体出生体质量新生儿 NEC 及降低其病死率,益生菌混合制剂的效果最优,可以作为益生菌预防方案的首选;双歧杆菌也较有优势,乳杆菌属次之,可依次作为次选;酵母属、芽孢杆菌属效果较去差,不建议单独使用。

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· 论著 ·

不同益生菌辅助治疗幽门螺杆菌感染疗效比较

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[摘要]**目的**:优选儿童幽门螺杆菌(Hp)感染的益生菌辅助治疗方案。**方法**:选取我院 2020 年 8 月至 2022 年 8 月收治的 Hp 感染患儿 120 例,按随机数表法分为试验组 1、试验组 2、试验组 3 和对照组各 30 例。四组患儿均采用常规三联疗法:口服克拉霉素(15 mg/kg,bid)+奥美拉唑肠溶胶囊(0.6~0.8 mg/kg,清晨顿服)+阿莫西林胶囊(25 mg/kg,大剂量 1 g,bid);另外,试验组 1 加用复合乳酸菌胶囊(1 粒,tid),试验组 2 加用双歧杆菌三联活菌胶囊(1 粒,tid),试验组 3 加用布拉酵母菌散(1 袋,bid)。三联疗法治疗 14 d,益生菌连续治疗 1 个月。比较四组患儿临床疗效、炎性因子水平、胃蛋白酶水平、临床症状评分及不良反应发生情况。**结果**:治疗 1 个月后,四组患儿白细胞介素(IL)-6、肿瘤坏死因子(TNF)-α、超敏 C 反应蛋白(hs-CRP)、胃蛋白酶原Ⅰ(PGⅠ)及临床症状评分均降低,且试验组(尤其试验组 2)低于对照组(P 均<0.05);胃蛋白酶原Ⅱ(PGⅡ)和胃蛋白酶原比值(PGR)均升高,且试验组(尤其试验组 2)高于对照组(P 均<0.05)。试验组(尤其试验组 2)总有效率高于对照组(P<0.05)。四组患儿不良发生率为 6.67%~13.33%,差异无统计学意义(P>0.05)。**结论**:采用双歧杆菌三联活菌辅助三联疗法治疗儿童 Hp 感染临床效果显著,可有效减轻炎性反应,调节胃蛋白酶平衡。

[关键词]益生菌;幽门螺杆菌;三联疗法;双歧杆菌三联活菌
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Comparison of Efficacy of Different Probiotics in the Treatment of Children with *Helicobacter Pylori* Infection

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[**Abstract**] **Objective**: To optimize the adjuvant therapy of probiotics in the treatment of *Helicobacter pylori* (Hp) infection in children. **Methods**: A total of 120 children with Hp infection admitted into the hospital from Aug. 2020 to Aug. 2022 were extracted to be divided into the control group, experimental group 1, experimental group 2, and experimental group 3, with 30 cases in each group. All groups received conventional triple therapy: oral clarithromycin (15 mg/kg, bid) + omeprazole enteric-dissolved capsules (from 0.6 to 0.8 mg/kg, morning meal) + amoxicillin capsules (25 mg/kg, maximum dose 1 g, bid). Meanwhile, experimental group 1 was given compound *Lactobacillus* capsules (1 capsule, tid) based on conventional triple therapy, experimental group 2 was given *Bifidobacterium* triple viable bacteria capsules (1 capsule, tid), and experimental group 3 was given *Saccharomyces boulardii* sachets (1 bag, bid). All patients were treated with triple therapy for 14 d and probiotics for 1 month. The clinical efficacy, levels of inflammatory factors, pepsin levels, clinical symptom scores and incidence of adverse drug reactions among 4 groups were compared. **Results**: After 1 month of treatment, the levels of interleukin (IL)-6, tumor-necrosis factor (TNF)-α, hypersensitive C-reactive protein (hs-CRP), pepsinogen Ⅰ (PGⅠ) and clinical symptoms scores in 4 groups decreased significantly, and the experimental groups (especially the experimental group 2) were lower than those of the control group (P<0.05); the levels of pepsinogen Ⅱ (PGⅡ) and pepsinogen ratio (PGR) in 4 groups increased significantly compared with those before treatment, and the experimental groups (especially the experimental group 2)

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