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Probiotics in *Helicobacter pylori*-induced peptic ulcer disease

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A B S T R A C T

The ideal treatment regimen for the eradication *Helicobacter pylori* infection has yet to be identified. Probiotics, particularly Lactobacillus, Bifidobacterium and Saccharomyces, have been suggested as adjuncts to antibiotics for the treatment of *H. pylori*. There is *in vitro* evidence that probiotics dampen the Th1 response triggered by *H. pylori*, attenuate *H. pylori* associated hypochlorhydria and secrete bacteriocidal metabolites. Probiotics interact with the innate host immune system through adherence to the gastric epithelium and secretion of bacterial adhesins. In prospective human studies, probiotic monotherapy effectively decrease *H. pylori* density (expired $^{13}CO_2$) by 2.0%–64.0%. Probiotic monotherapy has also been shown to eradicate *H. pylori* in up to 32.5%, although subsequent recrudescence is likely. Eleven meta-analyses have evaluated the efficacy of probiotics as adjuvants to antibiotics for the eradication of *H. pylori*. The addition of a probiotic increased treatment efficacy, OR 1.12–2.07. This benefit is probably strain-specific and may only be significant with relatively ineffective antibiotic regimens. The pooled prevalence of adverse effects was 12.9%–31.5% among subjects receiving adjuvant probiotics, compared with 24.3%–45.9% among controls. Diarrhea in particular was significantly reduced in subjects receiving adjuvant probiotics, compared with controls (OR 0.16–0.47). A reduction in adverse events other than diarrhea is variable. Despite the apparent benefit on efficacy and side effects conferred by probiotics, the optimal probiotic species, dose and treatment duration has yet to be determined. Further

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studies are needed to identify the probiotic, antibiotic and patient factors which might predict benefit from probiotic supplementation.

Introduction

Helicobacter pylori (*H. pylori*) is a ubiquitous Gram negative, flagellated, spiral organism which survives in the mucus layer overlying the gastric mucosa. Chronic *H. pylori* infection affects approximately 50% of the world's population. *H. pylori* has been etiologically linked to peptic ulcer disease, gastric MALT lymphoma and gastric adenocarcinoma. Eradication of *H. pylori* infection can be challenging, and despite over 30 years of experience in treating the organism, the ideal treatment regimen has not yet been identified. Pitfalls associated with unsuccessful treatment include antibiotic resistance, increased bacterial virulence, adverse drug reactions and various pharmacokinetic and pharmacodynamics factors such as drug–drug interaction and host CYP2C19 polymorphism. Over the past decade there has been surging interest in agents which might increase the likelihood of successful *H. pylori* eradication, including probiotics.

Although the gastric mucosa was long-considered sterile, owing to its acid milieu, the normal human stomach in fact has a rich microbiota [1]. The microbial load is lower in the stomach compared to other parts of the gastrointestinal tract [2] and the predominant phyla are Actinobacteria (including Bifidobacterium), Bacteroidetes, Firmicutes (including *Lactobacillus* spp), and Proteobacteria (including *Helicobacter* spp.) [3–5]. While the interaction of *H. pylori* with host immune pathways and intracellular signaling has been well described, the precise roles of the other components of the gastric microbiota remain elusive [6]. The composition of the gastric microbiota changes in the setting of *H. pylori* infection and other gastric pathologies. This underscores the potential for the therapeutic use of probiotics to restore the normal gastric microbiota [3]. The most commonly used probiotic bacteria belong to the genera Lactobacillus (L.) and Bifidobacterium (B.), and often also include yeasts such as Saccharomyces (S.) *boulardii* [7].

Pathophysiological basis for probiotic therapy

H. pylori

H. pylori infection causes gastric mucosal damage via various mechanisms. Firstly, *H. pylori* leads to hypochlorhydria. This is achieved by *H. pylori cag*-pathogenicity island gene products (such as CagL) which induce NFκB binding to the H+,K+-ATPase α (HK α) subunit gene promoter, leading to decreased HKα transcription and decreased acid secretion [8]. CagL triggers ADAM17-dependent release of heparin binding epidermal growth factor (HB-EGF), EGF receptor (EGFR) stimulation, ERK1/2 kinase activation, and NF-κB-mediated repression of HKα.

H. pylori can also directly activate neutrophils and monocytes, which in turn produce IL-1β and TNF-α. Both IL-1β and TNF-α are potent inhibitors of gastric acid [9]. *H. pylori* is able to penetrate the mucus layer and access the gastric mucosa by elevating gastric pH through secretion of urease, thereby reducing the viscosity of gastric mucus [10]. *H. pylori* BabA and SabA adhesins bind to Lewis B blood group antigens on mucin-5AC and can inhibit mucin assembly through inhibition of galactosyltransferase (the enzyme responsible for mucin side-chain assembly) and through silencing of trefoil factor-2 [11–13]. At the epithelial cell surface, the pore-forming vacuolating cytotoxin A (VacA) is internalized and disrupts intracellular metabolic pathways, increases membrane permeability and ultimately stimulates a pro-inflammatory Th1 response involving IL-2, IL-6, IL-8 as well as IL-1β and TNF-α, as described [14].