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Why Do ACG and AGA Guidelines Differ for the Use of Probiotics and the Prevention of CDI?

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In the recent publication of the American College of Gastroenterology (ACG) guidelines for *Clostridioides difficile* infections (CDI), Kelly et al. (1) recommended against probiotics for primary prevention of CDI (conditional recommendation, moderate quality of evidence) and probiotics for preventing CDI recurrences (strong recommendation, very low quality of evidence). These ACG guidelines failed to account for the strain specificity associated with probiotic efficacy by basing their conclusions on data pooling disparate types of probiotics together, which often results in a biased efficacy measurement. When different probiotics are analyzed accounting for strain specificity, some strains show significant efficacy, whereas others do not (2). In addition, Kelly et al. based their recommendations on only 1 underpowered randomized trial (RCT) to detect a significant effect on CDI and several meta-analyses that did not account for strain specificity. When the American Gastroenterology Association published their guidelines for CDI, they reviewed 39 RCTs, accounted for strain specificity in their analysis, and determined 4 different types of probiotics could be recommended for CDI (3). Both guidelines point out the need for more RCTs of probiotics for CDI to increase the strength of the evidence for both primary and secondary prevention of CDI.

Challenges for doing RCTs include the sporadic nature of CDI outbreaks and varying incidence of CDI at different healthcare facilities, leading to underpowered trials when the incidence of CDI is <5%. In an effort to test whether probiotics can be an effective adjunct to infection prevention programs, several studies have performed quasiexperimental studies where a specific probiotic is offered to inpatients at high risk of CDI (receiving antibiotics) and given for the duration of the patient's stay. Then, healthcare facility-level CDI rates are compared for periods before and during the probiotic intervention. Although not an RCT and lacking a concurrent control group, this approach has been successful in some programs for reducing CDI rates (4).

The guidelines from ACG also recommended fecal microbial transplants (FMT) for severe/fulminant CDI (strong recommendation, low quality of evidence) (1). However, instead of the recommendations being based on the gold standard (RCT), they are based on 7 studies: case reports/series and phase 2 formulation studies. These studies were not included as evidence for their analysis of probiotics and are typically excluded from efficacy analyses altogether, so it is unclear why these were included just for FMT. In addition, to prevent recurrent CDI, Kelly et al. based their positive recommendation on 12 studies, but only 3 are phase 3 RCTs. The authors concluded that there are "ample data demonstrating the safety and efficacy of FMT…," but the ample data do not include phase 3 efficacy RCTs. There seem to be different degrees of evidence required for the efficacy of probiotics and FMT.

The differing conclusions of these 2 guidelines highlight the effect of applying different types of evidence to evaluate distinct interventions and the impact of not accounting for probiotic strain specificity.

CONFLICTS OF INTEREST

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Response to McFarland et al.

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We appreciate the communication from McFarland et al. (1) (and note their disclosure that all serve on the Scientific Advisory Board for Bio-K+ International) but stand by our recommendations against probiotic treatment for the prevention of either primary or secondary *Clostridioides difficile* infections (CDI) and the unbiased

date analysis of the best available data, which underlies the same. For example, PLACIDE, the highest quality randomized controlled trial (RCT) thus far of probiotics for primary prevention of CDI, enrolled 2,800 high-risk elderly hospitalized patients receiving antibiotics and found no difference (2). If still underpowered at 2,800 patients, what is the number needed to treat to prevent 1 case of CDI? Practically speaking, the marginal benefit, if any, of routine probiotic use for primary prevention is low. We note that the American Gastroenterological Association recommendations (3), although conditionally supportive of probiotic use, do not differ dramatically from our own and clearly indicate that the quality of evidence for this indication is low, stating that the certainty of evidence was downgraded from moderate to low because of unclear or high risk of bias in 37 of 39 trials for all outcomes assessed. Their Technical Review Panel also cited concerns around potential publication bias, unusually high baseline risk in the few trials that weighed effects heavily, and wide confidence intervals. Regarding the letter authors' principal contention that we had not adequately analyzed probiotics according to substrains, the evidence is still too poor to change the recommendation. In fact, Dr. McFarland's own meta-analysis does not take studies' risk of bias into consideration, thus itself being susceptible to a potentially biased interpretation of the data. Although *Saccharomyces boulardii* showed some benefit in meta-analysis, none of the individual studies showed benefit, and if the studies that included high risk of bias in at least 2 domains are removed, there was no longer a benefit. The suggested 2-species efficacy was largely driven by a single study (4). Two other included studies had some uncertain risk of bias and at least 1 domain with high risk of bias (5,6). The suggested 3- and 4-species efficacies were driven by single studies with much uncertain risk of bias (7,8). In addition, the authors chose not to cite results from a recent study, evaluating a computerized clinical decision support tool to prescribe probiotics for primary prevention of CDI among adult hospitalized patients (9). This intervention, using the same 3-strain probiotic they advocate, completely failed to prevent primary CDI. In fact, incidence of CDI was higher in the postintervention group compared with the preintervention group, and although not statistically significant, CDI risk was greater among patients who received probiotics vs patients who did not. Further high-quality studies would be helpful in clarifying the role of probiotics for primary and secondary prevention in high-risk patients, and we encourage probiotic manufacturers, such as Bio-K+ international, to support such investigations. Until and unless such data emerge, we affirm our methodology and conclusions. Unlike probiotics, fecal microbiota transplant has been consistently and highly effective prevention of recurrent CDI in multiple RCTs (10) with clearer mechanisms of effect (11,12). Evidence is mounting to support fecal microbiota transplant in severe/fulminant infections as well (13), although the level of evidence is low for this indication, and we agree that further RCTs are needed to define best treatment protocols.

CONFLICTS OF INTEREST

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