Advances and Limitations of Evidence-Based Medicine – Impact for Probiotics

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Introduction

Evidence-based medicine recommends performance of randomized controlled trials (RCTs) and systematic reviews (or meta-analyses) of RCTs when addressing questions regarding the effects of therapeutic and prophylactic interventions. They are now a well-established means of reviewing existing evidence and integrating findings from various studies.

What Is a Systematic Review? What Is a Meta-Analysis?

Although the terms ‘systematic reviews’ and ‘meta-analyses’ are commonly used interchangeably, there is a distinction between the two. As defined by the Cochrane Collaboration [1], a systematic review is ‘a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyze data from studies that are included in the review. Statistical methods may or may not be used to analyze and summarize the results of the included trials’. A ‘meta-analysis’ is a name that is given to any review article when statistical techniques are used in a systematic review to combine

the results of included trials to produce a single estimate of the effect of a particular intervention (i.e., a number or a graph) [1]. There are 2 major reasons why a meta-analysis is performed within a systematic review. The first is to increase the power, i.e. the chance to reliably detect a clinically important difference if one actually exists. The problem with many individual studies is that they are too small to detect little effects, which can only be observed if the data from several trials are combined. The second reason is to improve precision in estimating effects, i.e. narrow the confidence interval around the effect [1].

Published Meta-Analyses on the Effects of Probiotics

A Pubmed search in December 2009 of the words ‘meta-analysis’ or ‘systematic review’ and ‘probiotics’ yielded a substantial number of papers, many of which are Cochrane reviews (table 1). To date, the most extensively studied applications and the best-documented areas of efficacy of probiotics are the treatment of acute infectious diarrhea and the prevention of antibiotic-associated diarrhea (AAD). For the first indication, evidence from several meta-analyses of RCTs has consistently shown a sta-

Table 1. Published meta-analyses on the effects of probiotics

Condition	References	Effect of probiotics
Acute gastroenteritis (treatment)	[5–10]	Approximately 1-day reduction in the duration of diarrhea; effect was strain and dose dependent
Antibiotic-associated diarrhea (AAD)	Children only: [11–13] Adults and children: [14–17]	Beneficial effect of selected probiotics in the prevention of AAD; the use of probiotics with documented efficacy, in appropriate doses confirmed in controlled trials, is probably acceptable whenever preventing this usually self-limited complication is important
<i>Clostridium-difficile</i> -associated diarrhea	[18–20]	Conflicting study results
Traveler's diarrhea (TD)	[21, 22]	Opposite study results
Necrotizing enterocolitis	[23–25]	Reduced the risk of severe necrotizing enterocolitis and mortality in preterm infants who were born <1,500 g
<i>Helicobacter pylori</i> infection	[26]	Improved eradication rates and reduced therapy-related side effects
Functional gastrointestinal disorders	[27]	No evidence that lactobacillus supplementation is effective
Irritable bowel syndrome	[28–32]	In single-organism studies, lactobacilli do not appear to be effective; bifidobacteria and certain combinations of probiotics demonstrate some efficacy
Induction of remission in Crohn's disease	[33]	Insufficient evidence
Maintenance of remission in Crohn's disease	[34]	No evidence to suggest that probiotics are beneficial to the maintenance of remission in Crohn's disease
Induction of remission in ulcerative colitis	[35]	Limited evidence suggests that probiotics added to standard therapy may provide modest benefits
Pouchitis	[36, 37]	Reduced risk of pouchitis; the most promising agent was VSL#3
Constipation	[38]	Until more data are available, the use of probiotics should be considered investigational
Allergy prevention	[39, 40]	Opposite study results
Respiratory tract infections (RTIs)	[41]	May have a beneficial effect on the severity and duration of symptoms of RTIs but do not appear to reduce the incidence of RTIs

tistically significant effect and moderate clinical benefit of *some* probiotic strains in the treatment of acute watery diarrhea, mainly rotaviral, primarily in infants and young children. Given the available evidence, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the European Society of Paediatric Infectious Diseases Expert Working Group [2] recently stated that selected probiotics with proven clinical efficacy (e.g. *Lactobacillus* GG, *Saccharomyces boulardii*) that are administered in appropriate dosages, according to the strain and the patient population, may be used as an adjunct to rehydration therapy for the management of acute gastroenteritis in children. Other probiotic strains may also be used provided their efficacy is documented in high-quality RCTs. Regarding the second indication, several systematic reviews, with or without a meta-analysis, have shown most of the tested probiotics to be effective in reducing the risk of AAD in the general (mainly adult) population and in children. For other disease states, although some preliminary results with probiotic use are promising, studies documenting clear effects are limited.

Is a Meta-Analytical Approach Appropriate to Assess the Efficacy of Probiotics?

Evaluation of the results of published meta-analyses reveals that, with few exceptions, probiotics administered for the treatment of a specific disease or condition are all evaluated together. The following question remains: is it appropriate to pool data on different probiotic microorganisms? It is tempting for the reviewers to produce a single estimate of the treatment effect. However, the results of a meta-analysis of all probiotics, regardless of the microorganisms used, may be misleading if appropriate consideration is not given to the interpretation of the pooled results.

Arguments for Pooling Data

The value of performing a meta-analysis is that by combining trials, the sample size is increased and, thus, the power. Pooling data on different probiotics allows one to (1) establish whether there is evidence of an effect; (2) determine the direction of the effect (3) determine the size of the effect (and the 95% confidence interval around

the effect); (4) assess the consistency of the effect across studies, and (5) identify the most promising probiotic(s). If many trials exist involving the administration of different probiotics to different participants with similar results consistently being seen in the various trials, the effect of the probiotic(s) has some generalizability. In addition, pooled data on different probiotics are important for demonstrating whether further research on these probiotics is substantiated. If so, these pooled data potentially may help identify the most promising microorganisms as well as the research questions to be addressed in future studies.

Arguments against Pooling Data

There are a number of arguments against pooling data. First, there is evidence that the beneficial effects of probiotics, particularly the immunomodulatory effects of individual probiotics observed in the host, differ greatly and are strain specific [3]. Second, probiotics vary by organism. In addition to the most commonly used lactic acid bacteria (e.g. lactobacilli, bifidobacteria), the yeast *S. boulardii* is often used. All of these probiotics have different properties and antipathogenic mechanisms. Consequently, their efficacy may vary. Third, the dose of probiotics may be important, as has been documented [4].

What Could Be the Solution?

Given these concerns, the best approach would be to perform a meta-analysis evaluating the effect of administering a clearly defined, single-organism, probiotic preparation or an equally well-defined combination of probiotic microorganisms for the treatment of a specific disease or condition. However, a lack of available

data often makes this infeasible. With few exceptions, only seldom are there data from more than single studies on a given probiotic microorganism or combination of probiotic microorganisms. Another commonly used approach is to perform a review of all probiotics and then to perform subgroup analyses based on factors considered a priori that could potentially influence the magnitude of the treatment response. Examples of such factors are the following: (1) the type of probiotic administered; (2) whether the probiotic was live versus dead; (3) the medium, and (4) the study population (children, adults).

Summary and Key Messages

Systematic reviews, with or without a meta-analysis, are now a well-established means of reviewing existing evidence and integrating findings from various studies.

The best-documented areas of efficacy of probiotics are the treatment of acute infectious diarrhea and the prevention of AAD.

Meta-analyses on probiotics provide valid information. However, caution should be exercised not to overinterpret the results of a meta-analysis when all probiotics have been evaluated together. Considering that the effects of probiotics are strain specific as well as population specific, they cannot be generalized.

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