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Treating acute infectious diarrhoea: use of probiotics no longer supported by the evidence?

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Question

Are probiotics effective in shortening the time until symptom resolution in proven or presumed cases of acute infectious diarrhoea?

Context

Infections of the gut by viruses, bacteria and parasites can cause acute diarrhoea. While acute diarrhoea usually spontaneously resolves within a few days, it can cause severe dehydration and even death. Rehydration is the key treatment. Certain probiotics, which are “friendly” bacteria and yeasts, are thought to be able to restore the natural balance in the gut after disruption due to illness and possibly reduce the duration and intensity of symptoms. It has been proposed that certain “core” mechanisms (e.g. competitive exclusion of pathogens) might be present in many probiotics, with other mechanisms possibly being species or strain specific. Nonetheless, their effectiveness in the treatment of acute infectious diarrhoea remains in doubt.

An update of an existing Cochrane systematic review on probiotics for acute infectious diarrhoea was performed (Collinson 2020). The earlier version of this review, published 10 years ago, was based on many small studies (Allen 2010). It indicated that probiotics shortened the mean duration of diarrhoea and reduced the number of children with diarrhoea lasting four days or longer.

Criteria for study selection

This updated review included studies comparing a specified probiotic compared to placebo or no probiotic in people with acute diarrhoea which was proven or presumed to be infectious in nature. The main outcomes were diarrhoea lasting 48 hours or more and the duration of diarrhoea.

Summary of the results

In total, 82 studies with 12.127 participants were included in the review. This included 11.526 children (younger than 18 years) and 412 adults as well as 189 adults and children whose age group was not specified. Most of the studies (53 studies) were performed in countries where both child and adult mortality were low or very low, and 26 studies in countries where child or adult mortality was high with three studies recruiting from populations crossing the mortality data.

The risk of bias was high or unclear in many studies. Moreover, when the studies were statistically combined in a meta-analysis, there was large diversity in effect sizes. This heterogeneity could not be explained by type of probiotic, type of participant (age, high vs low mortality risk, region of the world), diarrhoea in children caused by rotavirus, exposure to antibiotics or treatment with zinc. However, statistical tests and funnel plots showed that results of small studies differed from those of large studies for the main outcomes of this review. This tendency for effect estimates to differ between small and large studies is called small-study effects. This can be due to several reasons including poor methodological quality leading to spurious inflated effects in smaller studies and publication bias for example. The review authors think it is likely that publication bias occurred in this case. Publication bias results from the failure to publish certain studies based on the direction or the strength of their results. Failure of inclusion of unpublished studies can, thus, lead to skewed effect estimates. In this review the many small studies showed positive effects of probiotics, while larger, more recent and well-conducted studies showed null effects. This suggests that the small studies which showed no effect (or even harmful effects) of probiotics were never published or published in small, non-English journals which are often difficult to search.

For the above-mentioned reasons, the review authors decided to only include studies with low risk of bias (i.e. scoring "low" on all 6 items of the Cochrane Risk of bias assessment tool) in their main analyses. This considerably reduced the number of studies from 82 studies to 7 studies (and thus the number of different probiotic strains) which could be included in the analyses. The use of probiotics probably results in little or no difference in the number of people with diarrhoea for 48 hours or longer (placebo: 536 per 1000 vs probiotics: 536 per 1000 (95% CI*: 488-584); 2 studies, 1770 participants, moderate-certainty evidence). Both North American studies were published in 2018, were similar in design and assessed the effects of *L. rhamnosus* GG (LGG) or a different strain of *L. rhamnosus* in combination with *L. helveticus*. We are uncertain of the effect of probiotics on the mean duration of diarrhoea (MD^: 8.64 hours lower (95% CI: 29.38 hours lower to 12.1 hours higher); 6 studies, 3058 participants, very low-certainty evidence). These studies were done either in India (3/6) or North-America (3/6) and investigated LGG (4/6), *L sporogenes* (1/6) or a combination of *L. rhamnosus* Rosell-11 and *L. helveticus* (1/6).

For the secondary outcomes of this review, the meta-analyses were not restricted to low risk of bias studies alone and the certainty of the evidence was not assessed. Results suggest that there is no evidence that probiotics reduced risk of hospitalization or risk of diarrhoea lasting 14 days or longer, but they may reduce duration of hospitalisation. No serious adverse events were reported among people who took probiotics.

Conclusion

The conclusions of this updated review differ from that of the previous version, which may be due to publication bias in the previous version. Small studies had mostly positive results and probably skewed the analyses in the previous version of this review. Current analyses based on two large trials

with low risk of bias show that probiotics (more specifically strains of *L. rhamnosus* with or without *L. helveticus*) probably make little or no difference in the number of people with diarrhoea lasting 48 hours or longer. We remain uncertain of their effect on the duration of diarrhoea. The review authors state that the heterogeneity in this review and other reviews on the topic argues against the presence of "core" properties shared by different probiotics that are active against diarrhoea due to several infectious agents. Future research should focus on probiotics with properties that address specific pathogenic mechanisms, probably limiting them to certain infectious agents or populations.

Implications for practice

While the ESPGHAN guidelines of 2014 recommend the use of LGG and *Saccharomyces boulardii* (strong recommendations, low-quality evidence), as well as *L. reuteri* and *L. acidophilus* (weak recommendation, very low-quality evidence), the results of this review show that one needs to be careful when formulating recommendations based on evidence from mostly small low-quality studies. The findings of this review suggest that at least the guideline for LGG needs to be reviewed as the current evidence does not support its use for the treatment of acute infectious diarrhoea.

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* **CI:** confidence interval
^ **MD:** mean difference