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No benefit found for use of probiotic Bifidobacterium breve to prevent death, late-onset sepsis

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The results of a phase 3 randomised controlled trial, published today in *The Lancet*, show that, despite being safe to administer, there is no benefit in using the probiotic Bifidobacterium breve (BBG-001) to prevent late-onset sepsis or necrotising enterocolitis in very preterm children.

Between July 1, 2010, and July 31, 2013, 1315 infants were recruited for the study; of whom 654 were allocated to probiotic and 661 to placebo. Rates of the primary outcomes did not differ significantly between the probiotic and placebo groups. 61 infants (9%) in the probiotic group had necrotising enterocolitis compared with 66 (10%) in the placebo group; 73 (11%) infants in the probiotics group had sepsis compared with 77 (12%) in the placebo group; and 54 (8%) deaths occurred before discharge home in the probiotic group compared with 56 (9%) in the placebo group. No probiotic-associated adverse events were reported.

"The results of this trial contrast with the conclusions of the meta-analysis in the Cochrane review that report significant reductions in necrotising enterocolitis and mortality associated with probiotic administration", write the authors.

The authors stress that there were no safety issues with the probiotic preparation used in this study. However, they caution that "Possibly more worrying is the possibility of contamination of products,

highlighted by a health alert issued in 2014 following the reporting of a case in the USA of fatal fungal infection in a preterm infant attributed to contamination of the product used in two published trials. This serves as a reminder that most probiotic products are not produced to pharmaceutical standards and that their unregulated use outside a trial protocol might not be risk free."

Neither this study, nor the previously published ProPrems study using different probiotic interventions, have shown efficacy to prevent sepsis or death. Although ProPrems did show reduced necrotising enterocolitis, this was in a setting with low background rates of this complication. The authors say: "These two large trials suggest that, while probiotics are generally safe in the short term, they are not universally effective, and that different strains and combinations should be investigated separately."

They conclude: "The importance of gut microbes in the complex pathogenesis of necrotising enterocolitis is widely accepted. As understanding progresses so the rationale for the choice of probiotics that might have a therapeutic role either alone or in combination, and of which infants might benefit, should strengthen. In the meantime, the evidence from this trial does not support the routine administration of probiotics to the preterm infant and the validity of combining trials of different probiotics to perform meta-analyses must be questioned."

Writing in a linked Comment, Dr Thomas Abrahamsson, Division of Paediatrics, Linköping University, Sweden, says: "These findings stress the fact that only probiotic strains that have been proven effective in clinical trials should be used in clinical practice. Also, they emphasise that general recommendation of a treatment always should be preceded by randomised controlled trials with high level of quality. Meta-analyses with substantial heterogeneity of the included trials are not sufficient."

More information: *The Lancet*, www.thelancet.com/journals/lan … (15)01027-2/fulltext