Probiotics to prevent necrotising enterocolitis in preterm infants

A Cochrane review reported that prophylactic use of probiotics reduced the risk of severe necrotising enterocolitis and death in preterm infants.

Overview: Necrotising enterocolitis is characterised by inflammation and death of patches of bowel wall in newborn babies. Most cases of necrotising enterocolitis occur in preterm infants (Holman et al. 2006), in particular in very low birth weight infants (<1500 g). The cause of necrotising enterocolitis is unclear, but the condition is thought to be related to intestinal immaturity, an underdeveloped immune system and colonisation of the intestine by pathogenic bacteria (Tanner et al. 2014).

Probiotics are supplements containing live bacteria that colonise the gastrointestinal tract and are intended to beneficially alter the balance of gut microorganisms in the host. Probiotics could potentially reduce the risk of necrotising enterocolitis in preterm infants by competing against potential pathogens, preventing migration of bacteria and their products across the intestinal mucosa, and enhancing immune responses (Patel and Denning 2013).

Current advice: Necrotising enterocolitis can be managed either medically or surgically, depending on disease severity (Neu and Walker 2011). Options for initial medical management include gastric decompression, bowel rest, and intravenous broad-spectrum antibiotics, fluids and nutrition.

Surgical interventions are usually required in infants with bowel perforation or deteriorating clinical or biochemical status (for example, a decreasing platelet count). Surgical procedures may involve primary peritoneal drainage, exploratory laparotomy with resection of the dead or diseased bowel, or enterostomy with creation of a stoma.

New evidence: A Cochrane review by AlFaleh and Anabrees (2014) assessed whether administration of probiotics prevented severe necrotising enterocolitis in preterm infants. A search was conducted for randomised and quasi-randomised controlled trials in preterm infants aged less than 37 weeks or who had a birth weight of less than 2500 g, or both. Studies had to compare enteral administration of any live probiotic, at any dose for more than 7 days, with placebo or no treatment. The primary outcomes were severe necrotising enterocolitis (stage II or more on Bell’s criteria), hospital-acquired sepsis (positive culture of blood or cerebrospinal fluid taken after 5 days of age), and all-cause mortality.
A total of 24 trials were identified, which included 2761 infants treated with probiotics and 2768 control infants. Compared with placebo or no treatment, use of prophylactic probiotics was associated with a significantly lower risk of severe necrotising enterocolitis in preterm infants (relative risk [RR]=0.43, 95% confidence interval [CI] 0.33 to 0.56, p<0.00001; 20 studies, n=5529). Probiotics were likewise effective at reducing severe necrotising enterocolitis in very low birth weight infants (RR=0.41, 95% CI 0.31 to 0.56, p<0.00001; 17 studies, n=4914).

Probiotics also reduced all-cause mortality (RR=0.65, 95% CI 0.52 to 0.81, p=0.00017; 17 studies, n=5112), but did not have a significant effect on the risk of sepsis (RR=0.91, 95% CI 0.80 to 1.03, p=0.12; 19 studies, n=5338). None of the included studies reported any cases of systemic infections caused by probiotics. Preparations containing either *Lactobacillus* species alone or a mixture of probiotics appeared to be most effective.

Limitations of this analysis include the heterogeneity of the included studies in: enrolment criteria; baseline risk of necrotising enterocolitis in the control groups; timing, dose and formulation of the probiotics; and feeding regimens. Only 11 of the 24 included trials were classified as high quality based on adequacy of allocation concealment procedures and blinding of the intervention. Insufficient data were available for analysis of the effect of probiotics in extremely low birth weight preterm infants (birth weight <1000 g).

**Commentary:** “Probiotic administration to neonates appears to be safe, cheap and readily implementable. Taking that into account, this Cochrane Review appears to make a convincing case for using these products in preterm neonates. However, probiotic administration is not yet used routinely on neonatal units.

“The case for routine probiotics has not been aided by initial data from a recently concluded large UK randomised controlled trial (PIPS) evaluating the use of *Bifidobacterium breve* BBG-001, which showed no advantage at all from the intervention (Costeloe et al. 2014). It would be naive to expect all probiotic bacteria to be equally effective; the risk of recommending routine use of probiotics at the present time is that we do not know which regimen should be used.

“What is needed to definitively answer this question is a very large trial comparing different probiotic agents. Such a trial would have to be carefully designed to avoid interference from cross-colonisation of infants on the same unit (as observed in some placebo-controlled probiotic trials; Hickey et al. 2014), and may be prohibitively expensive.” — Dr Jim Gray, Consultant in Microbiology, Birmingham Children’s Hospital and Birmingham Women’s Hospital

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