

New perspectives on probiotics in infant health



***Lactobacillus reuteri* DSM 17938 (*L. reuteri*): What is the evidence?**

Hania Szajewska, MD, PhD, Professor Department of Pediatrics, The Medical University of Warsaw, Poland

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. Here, the aim was to summarize the evidence on the efficacy of *Lactobacillus reuteri* DSM 17938, also known as *L. reuteri* Protectis.

Functional gastrointestinal disorders

Infantile colic. *L. reuteri* DSM 17938 works for managing infantile colic in breastfed infants as documented in two double-blind RCTs (Savino et al. Pediatrics 2010; Szajewska et al. J Pediatr 2013). Both RCTs found that the administration of *L. reuteri* DSM 17938 (10^8 CFU for 21 days) to exclusively or predominantly breastfed infants was associated with treatment success (defined as the percentage of children achieving a reduction in the daily average crying time >50%). Furthermore, in a systematic review, *L. reuteri* was effective for the treatment of colic in breastfed infants (Sung et al. JAMA Pediatr 2013).

Functional abdominal pain. One double-blind, placebo-controlled RCT conducted in 60 children (aged 6 to 16 years) with functional abdominal pain according to the Rome III criteria found that compared with placebo, children supplemented with *L. reuteri* DSM 17938 (2×10^8 CFU/day) had significantly lower pain intensity (Romano et al. J Paediatr Child Health 2010).

Functional constipation. One RCT conducted in 44 infants with functional chronic constipation found that infants in the probiotic group, compared with the placebo group, had a significantly

higher frequency of bowel movements at week 2 ($P=0.042$), week 4 ($P=0.008$), and week 8 ($P=0.027$) of supplementation. In the *L. reuteri* group, the stool consistency was reported as hard in 19 infants (86.4%) at baseline, in 11 infants (50%) at week 2, and in 4 infants (18.2%) at weeks 4 and 8 (Coccorullo et al. J Pediatr 2010).

Treatment & prevention of diarrheal diseases

Treatment of acute gastroenteritis. A recent meta-analysis (search date: August 2013) found that compared with placebo or no treatment, use of *L. reuteri* DSM 17938 significantly reduced the duration of diarrhea (mean difference -32 h, 95% CI -41 to -24) and increased the chance of cure on day 3 (RR 3.5, 95% CI 1.2 to 10.8) (Szajewska et al. Benef Microbes 2014).

Prevention of nosocomial diarrhea. One double-blind, placebo-controlled RCT conducted in 106 children (aged 1-48 months) found that administration of *L. reuteri* DSM 17938 at a dose of 10^8 CFU, once daily, for the duration of the hospital stay did not significantly affect the risk of developing nosocomial diarrhea, defined as 3 loose or watery stools per day in a 24-hour period that occurred >72 hours after admission (RR 1.06, 95% CI 0.7-1.5), or rotavirus infection (RR 1.04, 0.6-1.6) (Wanke et al. J Pediatr 2012). A new study, using a higher dose of *L. reuteri*, is underway.

Necrotizing enterocolitis (NEC) & sepsis

Two recent RCTs addressed the effects of use of *L. reuteri* DSM 17938 in preterm infants at risk for NEC or sepsis (Rojas et al. Pediatrics 2012; Oncel et al.

Arch Dis Child Fetal Neonatal Ed 2013). The pooled results from these 2 RCTs showed that compared with placebo, *L reuteri* DSM 17938 did not reduce the risk of NEC (2 RCTs, n= 1150, 0.69, 95% CI 0.38 to 1.26), reduced the risk of sepsis, although the difference was of a borderline statistical significance (RR 0.73, 95% 0.51 to 1.04), and significantly reduced the risk of feeding intolerance (RR 0.70, 95% CI 0.54 to 0.90) (Szajewska et al. Unpublished).

Ongoing studies

A search of the ClinicalTrials.gov website (search date: December 2013), a registry of clinical studies, for RCTs on *L reuteri* DSM 17938 that were registered but not yet published revealed 14 open

trials (i.e., studies that are currently recruiting participants or will be recruiting participants in the future).

In summary, *L reuteri* DSM 17938 is one of the probiotics that is well studied in double-blind, placebo-controlled RCTs. Evidence has now accumulated to support the consideration of the use of *L reuteri* DSM 17938 for the management of infantile colic in breastfed infants or for the management of acute gastroenteritis in children. However, additional basic research and clinical trials are still needed to fully define the role of *L reuteri* DSM 17938 in pediatrics. A number of such studies are underway.



Prevention of colic, constipation and regurgitation - possible role of probiotics.

Flavia Indrio, MD Senior Consultant Neonatologist Pediatric Gastroenterologist
Department of Paediatrics, University of Bari, Italy

Functional gastrointestinal disorders (FGID) are defined as a variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities.

Since FGIDs in childhood are age-dependent, the Rome Foundation established two different paediatric committees to identify the criteria for FGID diagnosis: the Infant/Toddler (up to 4 years) Committee and the Child/Adolescent Committee (aged 4 to 18 years).

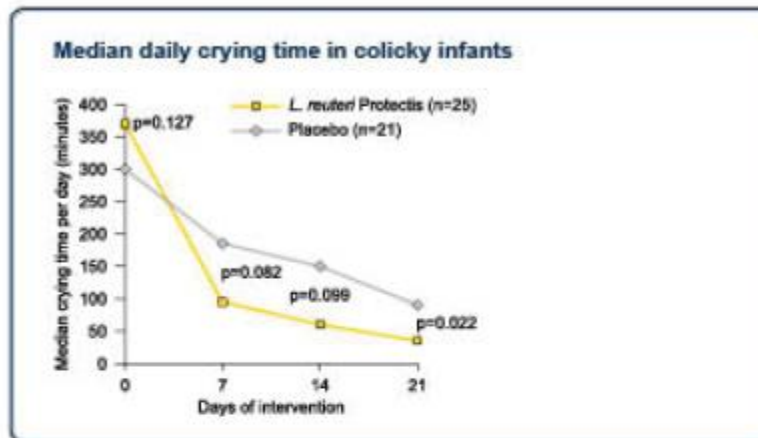
Infantile colic, gastro-esophageal reflux and constipation are the most common FGIDs that lead to referral to a paediatrician during the first six months of life and are often responsible for hospitalization, feeding changes, use of drugs, parental anxiety and loss of parental working days with relevant social consequences.

Although FGIDs have been considered as self-limited processes, it has already been shown that a low-grade mucosal inflammation and immune/motor alteration could be found in infants affected by colic, regurgitation and constipation. This early traumatic insult to the intestine may represent a

risk factor for the development of Irritable Bowel Syndrome (IBS) and psychological problems later in life. Recent work indicates a crucial role of the intestinal microbiota in the pathogenesis of gastrointestinal disorders as in FGID and there are many studies that target probiotic therapy for specific diseases such as colic, regurgitation and constipation. The effect of a probiotic could play a crucial role in modulation of intestinal inflammation.

Driving a change of colonization during the first weeks of life through giving lactobacilli may promote an improvement in intestinal permeability; visceral sensitivity and mast cell density and probiotic administration in a preventive way may represent a new strategy for preventing these conditions, at least in predisposed children.

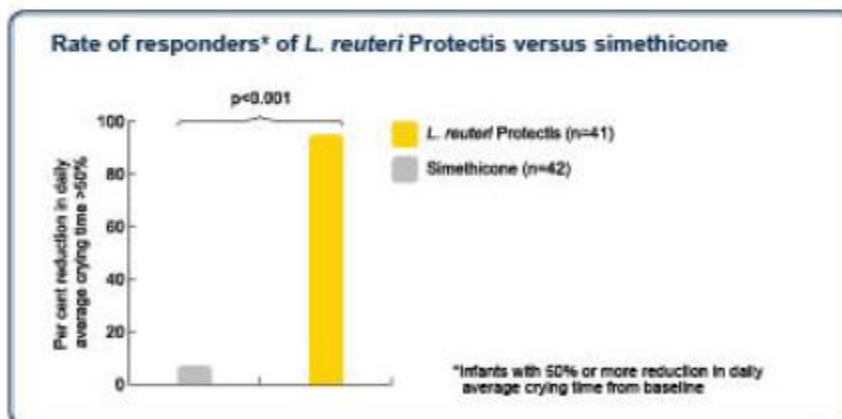
L. reuteri reduced crying time by more than 4,5 hours after one week



- * The effect was seen as early as one week after supplementation
- * Daily crying time was reduced by 1½ hours on average compared to placebo

Savino F et al. Pediatrics 2010;126:e526-e533.

95% of colicky infants responded to L. reuteri treatment



- * L. reuteri was superior to the currently most prescribed treatment simethicone in reducing daily crying time
- * L. reuteri reduced crying time by more than twice as much as simethicone

Savino F et al. Pediatrics 2007;119:124-130.