Pediatrics & Therapeutics
ISSN: 2161-0665
OPEN ACCESS Freely available online
Review Article

Gastroesophageal Reflux in Infants: A Review of Conventional and Emerging Therapy

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ABSTRACT

Gastroesophageal reflux is a common symptom in the infants. It is the common reason for which parents seek consultation of paediatricians. The present management of GER starts with position and feeding measures, followed by antacids and prokinetics. The clinical practices for management of Gastroesophageal reflux have been evaluated critically with safety, efficacy, and practical connotations. The evidence on Gastroesophageal reflux conventional therapies and *Lactobacillus reuteri* DSM 17938 was gathered from the PubMed and SCOPUS indexed journals with no language restriction till December 2019. The probiotic *Lactobacillus reuteri* DSM 17938 has also shown effective results in the treatment of Gastroesophageal reflux. It could be the upcoming therapy for treating Gastroesophageal reflux in infants.

The conventional therapies like the use of PPI, prokinetic agents, anti-regurgitation formula and body positioning of infants have a limitation in reducing regurgitation episodes. The conventional therapies had few adverse effects, and some were life threatening. In the case of L. reuteri DSM 17938 reduces daily reflux, enhances gastric motility, helps to increase body weight, promotes overall growth in infants.

Keywords: Infant, *Lactobacillus reuteri*, Probiotics, Gastroesophageal reflux

INTRODUCTION

Gastroesophageal reflux (GER) in infants is a common problem and counselling point for the physicians and paediatricians worldwide. GER is the involuntary passing of gastric Contents in to the esophagus and is often physiological. It commonly involves regurgitation, or "spitting up," which means the return of gastric contents retrospectively into the oesophagus. It is mainly seen in the infants between one to five months of age and usually resolves by six to 12 months of age [1,2].GER is a normal physiological process which occurs at daytime with repeated episodes in infants, children, and in adults. Mostly the GER episodes in healthy infants last <3 minutes, it is seen in the postprandial period, with or without symptoms [2, 3]. Parental anxiety leads to several visits to the physician and paediatricians. Etiology of GER is not properly defined [4]. It is seen in either genders. In modern practice it is treated with various pharmacological agents. Till date there is no specific therapy for GER and to term it as a disorder is controversial.

The human microbiota, specifically the intestinal microbiota has effects in various systems like immune regulation, metabolism and neuronal functions [5]. The various strains of the Lactobacillus species are used in children and adults [6].There is remarkable increase in research on *Lactobacilli* over past decade and there are more than 5700 research articles published during 2000-2014 on Lactobacillus. It is considered as an indigenous species of human gastrointestinal (GI) tract [7]. *L. reuteri* DSM 17938 has beneficial effects which include development of intestinal health, enhancement of signs of lactose intolerance, and decrease in the risk of various diseases including regurgitation, infantile colic, etc [8]. *L. reuteri* DSM 17938 is available in over 100 countries commercially [9].

The goal of this review is to understand the GER and the role of conventional and emerging therapies like of *L. reuteri* DSM 17938 as upcoming therapy. The information provided here is based on review of literature from Randomized Controlled Trials (RCTs). This review includes physiology of GER in infants, difference between GER and GERD (Gastroesophageal Reflux Disease), current management of GER and present evidence of role of *L. reuteri* DSM 17938 in the management of GER.

SEARCH METHODOLOGY

PubMed and SCOPUS indexed cited journals literature pursuit was conducted in December 2019 with no language restrictions,

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Received: December 27, 2020; **Accepted:** January 18, 2020**; Published:** February 6, 2021

Citation: Jog PP, Shinde VR, Sonawale SB, Veligandla KC (2021) Gastroesophageal Reflux in Infants: A Review of Conventional and Emerging Therapy. Pediatr Ther 10.380. doi:10.35248/2161-0665.20.10.380

for relevant randomized controlled trials (RCT) to identify the research and evidence that has been conducted up to that date on GER in infants and its various treatments and also with the *L. reuteri* DSM 17938 and to find the therapeutic effectiveness [3].

PHYSIOLOGY OF GER

The GER in infants occurs by Transient Lower Esophageal Sphincter Relaxation (TLESR). TLESR is a sudden reflex reduction in Lower Esophageal Sphincter (LES) below intragastric pressure, not related to swallowing. The infants have number of TLESR every day [10].

GER is a normal phenomenon in infants, which is worsened by liquid diet and age-specific body position [11,12]. GER is more commonly seen after a feeding; due to gastric distension [13].The body posture also affects TLESR and GER in infants. After feeding infants rested in the right side-down lateral position alter feeding have more TLESR episodes and the liquid reflux contrasted with the left side-down lateral position [14]. The GER episodes are also decreased with prone position as against supine position, likely because of more optimal positioning of the LES relative to the distended stomach [15].

DIFFERENCE BETWEEN GER AND GERD

The importance of differentiating GER from GERD cannot be underestimated from management point of view [3]. GER has been reported in 40 to 65 percent of healthy infants but decreases to one percent by a year of age [4].

GER becomes GERD when symptoms worsen (Table 1). GERD means symptoms or complications associated with pathological GER. GERD is reflux that produces troublesome symptoms for the patient (i.e., recurrent expressions of pain or unhappiness beyond the norm for the patient's age) and may lead to complications, such as reflux esophagitis, strictures, respiratory complications, failure to thrive, etc [16] (Table 1).

Table 1: GER and GERD clinical features.

GER	GERD
Regurgitation with regular weight gain	Regurgitation with inadequate weight gain
No clinical indications of esophagitis	Constant irritability; Lower chest pain in infants, dysphagia, pyrosis in children Hematemesis (blood in vomit) and anaemia (iron deficiency)
No significant respiratory symptoms	Apnea and cyanosis in infants Wheezing or recurrent pneumonia, Chronic cough Stridor
No neurobehavioral symptoms	Neck tilting is seen in infants (Sandifer's syndrome)

MANAGEMENT OF GER BY CONVENTIONAL THERAPY

As per the conventional therapy to treat GER, the management of GER starts with parental education and reassurance. Parents should be educated on how overfeeding may aggravate regurgitation. There are lifestyle modifications for infants to control GER, like left

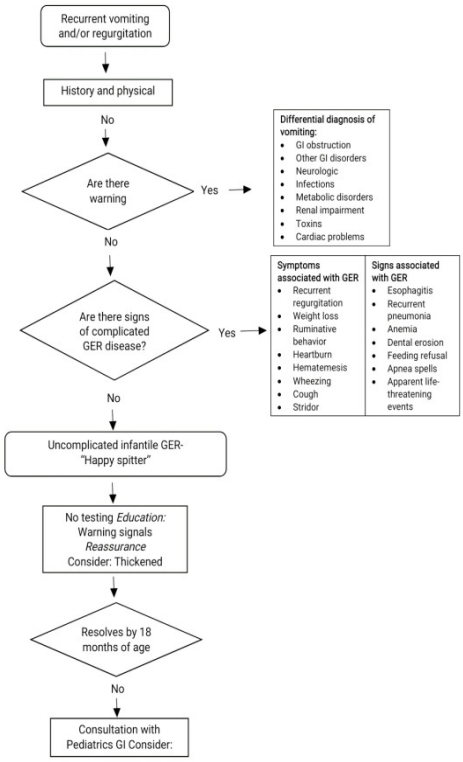

Figure 1: Algorithm for GER in infants' practical approach (Adopted from "Pediatric Gastroesophageal Reflux Clinical Guidelines") GER: Gastro-Esophageal Reflux, GI: Gastrointestinal, EGD: Esophagogastroduodenoscopy.

Table 2: Various treatments to treat GER

Author	Study details	Treatment	Outcomes
Salvatore S, et al. [19] (2018)	Prospective, observational study to assess the effectiveness of alginate to reduce GER episodes in infants	Alginate	The results suggest that alginate decreases the number and delay both acid and non-acid reflux episodes and associated symptoms in infants significantly.
Ummarino D, et al. [20] (2015)	Prospective randomized, open label, controlled trial to check the effect of Magnesium Alginate + Simethicone on GER in infants	Magnesium Alginate + Simethicone	Magnesium alginate + simethicone seems to be effective on GER symptom scores than thickened formula and with lifestyle changes alone.
Jadcherla SR, et al. [21] (2015)	Prospective study to evaluate the effects of feeding strategies (feeding volumes, durations methods and cycles, caloric density, milk types) and the duration between feeding sessions in premature neonates that undergone diagnostic evaluation for GER.	Feeding Strategy	Prolong feeding durations and slower flow rates decreases GER frequency. Change of feeding duration and flow rate can be a useful in dysphagic neonates.
Loots C, et al. [22] (2014)	Prospective sham-controlled trial, conducted on infants aged 0-6 months	PPI + LLP, PPI + HE, AA + LLP, or AA + HE.	PPI + LLP combination was effective in reducing GER episodes ($P<0.001$) and no other treatment group showed improvement in crying/irritability.

Corvaglia L, et al. [23] (2013)	RCT was carried out on 40 infants with age <33 weeks and intolerance feeding were fed 1-week eHPF diet	eHPF	The use of eHPF reduces esophageal acid exposure in preterm infants with feeding intolerance and with GER symptoms.
Corvaglia L, et al. [24] (2012)	RCT to evaluate by combined pH-MII the effect of a new preterm formula TPF on GER features in symptomatic preterm infants.	Starch-thickened preterm formula	The new formula was made to reduce the events of acid GERs by detecting with pH-monitoring; it neither reduced total esophageal acid exposure nor non-acid GERs.
Corvaglia L, et al. [25] (2010)	RCT was assessed to check the efficiency of sodium alginate (Gaviscon) for the treatment of GER in preterm infants	Sodium Alginate (Gaviscon)	The use of Gaviscon in preterm infants seems to decrease GER acidity and the advantage of a non-systemic way of action and a more favourable safety profile over histaminic 2 blockers and PPIs.
Hegar B, et al. [26] (2009)	Prospective RCT was performed on 20 infants. Domperidone versus Cisapride in the treatment of infant regurgitation and acid reflux	Domperidone versus Cisapride were provided after GER symptoms	The acid reflux decreased more in the cisapride group and decrease in regurgitation was seen in both groups.
Cresi F, et al. [27] (2008)	Prospective RCT to check short-term effect of domperidone on GER in newborns assessed by pH-MII	Domperidone	The paradoxical increase in GER events could be the expression of a domperidone-induced amplification of the motor incoordination of the neonatal GI tract.
Corvaglia L, et al. [28] (2007)	22 Premature infants with frequent regurgitation and postprandial desaturation underwent a 24-hour recording of pH-MII	Different positions: supine, prone, on the right side, and on the left side for 20 hr	infants in the prone or left lateral position in the postprandial period limits GER
Del Buono R, et al. [29] (2005)	Double Blind study was carried on 20 infants to examine the effect of Gaviscon infant on GER in infants using pH-MII	Sodium Alginate (Gaviscon)	Results showed significant difference between Gaviscon infant and placebo in average reflux height.
Garzi A, et al. [30] (2002)	20 infants were fed with breast milk, enrolled to assess the usefulness of an eHF in infants suffering from GER by dynamic echography	eHF	eHF led to a significant improvement (P= 0.0039) especially in babies skin-test

GER: Gastroesophageal Reflux, PPI: Proton Pump Inhibitor, LLP: Left Lateral Position, HE: Head of Cot Elevation, AA: Antacid, RCT: Randomised Control Trial, eHF: Extensively Hydrolysed Cow's Milk Formula, pH-MII : pH and Impedance Monitoring, TPF: Thickened with Amylopectin

lateral body position, head elevation. The pharmacological agents have also been used to treat GER in infants like acid suppressants (antacids, histamine-2 receptor antagonists (H2RAs), and PPIs) [17,18].

There are some studies on the thickened formula or 'Anti-Regurgitation Formula' (AR-formula) decreases the frequency and the volume of regurgitation. A subgroup of infants with GER who do not respond to traditional management may in fact suffer from Cow's Milk Protein Allergy (CMPA). Elimination of cow's milk protein decreases regurgitation and/or vomiting significantly within 2 weeks in these infants (Figure 1) [2,3].

The previous research carried out by the researchers with various treatments to treat GER is summarized in Table 2.

There are therapies which had their own drawback on the infants like Pantoprazole (Antisecretory agent) and Cisapride (prokinetic agent) failed to give beneficial effect. In some trials QT prolongation in infants was observed due to Cisapride Moreover, Proton pump inhibitors are not considered as first line therapy even in infants with severe reflux disease due to variable maturation of enzymes required for metabolism (CYP2C19 and CYP3A4) and reduced renal clearance in infants [40]. The left lateral body position has been recommended, but it is associated with an intermediate risk for sudden infant death syndrome between prone [19].

L. *REUTERI* DSM 17938 AS EMERGING THERAPY IN MANAGEMENT OF GER

L. reuteri DSM 17938 is the most extensively studied probiotic in children for functional gastrointestinal disorders. It is a probiotic isolated from humans; it is associated with health benefits and has shown to be safe for use in healthy infants [5]. Probiotic supplementation with *L. reuteri* is also associated with enhanced gastric motility in preclinical and clinical studies for regurgitation and GER [31].

MECHANISMS OF ACTION OF *L. REUTERI* DSM 17938 AND ITS EFFECT ON REGURGITATION

The adhesion of probiotic to the host GI tract is essential for colonization, to interact with host cells, to inhibit pathogen growth, and to protect epithelial cells or immune modulation. Some studies have shown *L. reuteri* capacity to colonize and have capability to adhere to the mucin and gastric epithelial cells. The possible mechanism of *L. reuteri* involves in adhesion linked to surface protein, mucus-binding protein, exopolysaccharide, inulosucrase, D-alanyl-LTA, and glucosyltransferase A [5] (Figure 2).

On gut motility *L. reuteri* DSM 17938 has influenced intestinal motility by anaerobic fermentation of carbohydrates and proteins which produces short chain fatty acids, acetate, butyrate, H2, CO2, amines. By increasing colonic myoelectric motility coplex frequency and velocity [3,5].

L. reuteri DSM 17938 had shown various actions, the evidence as antimicrobial activity by producing antimicrobial substances like hydrogen peroxide, lactic acid, reuterin and reuterin cyclin. Effectively preventing oxidative damage caused by free radicals. An anti-inflammatory action of *L. reuteri* had shown in vivo animal studies by reduction of intestinal mucosal levels of pro-inflammatory cytokines (interleukin-8 (IL-8), IL-1α, interferon-α, TNF-α) in newborn rats with LPS-induced small intestinal and ileum inflammation. *L. reuteri* DSM 17938 has also shown effect by acting as a visceral anti-nociceptive agent [3,5].

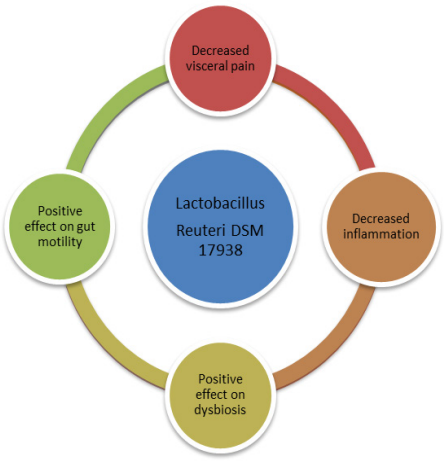

Figure 2: Mechanism of *L. reuteri* DSM 17938.

THE STUDIES PERFORMED ON *L. REUTERI* DSM 17938

Deshpande G, et al., conducted a prospective observational study and found that after using *L. reuteri,* exclusive with omeprazole use to treat GER cases. A drop from 31/205 to 16/188 in preterm neonates <30 weeks was seen. American Academy of Pediatrics strongly advice gastric acid blockading agents should be used sparingly, if at all, in preterm Infants. As an adjuvant therapy new Pro-kinetic Probiotic L. reuteri DSM 17938 was introduced in the Nepean NICU in 2017 [32].

Cui X, et al., performed a double-blind Randomised Control Trial (RCT) to evaluate the effects of *L. reuteri* DSM 17938 in infants aged between 30- 37 weeks and weighed 1.5- 2 kgs (kilograms) were included in the study, each group consist of 57 infants. As the therapy continued in interventional group *L. reuteri* DSM 17938 had decreased regurgitation episodes by 2.18 ± 0.83 *vs* 3.77 ± 0.66, $p < .01$, daily weight gain was 14.55 ± 3.07 g/d *vs* 10.12 ± 2.80 g/d, head circumference increase 0.0760 ± 0.0157 cm/d *vs* 0.0681 ± 0.0108 cm/d, body length increase 0.1878 ± 0.0151 cm/d vs. 0.1756 ± 0.0166 cm/d of the intervention group were higher than control group $p < .01$. During study there were no ADR were reported [33].

A double blind RCT was carried out by Indrio F, et al., to check the effects of partially hydrolysed, 100% whey protein, starch and *L. reuteri* DSM 17938 formulae in 72 infants with functional regurgitation with GER, to check gastric emptying rate and frequency of regurgitation. It was observed that changes in gastric emptying rate (12.3% in test group and 9.1% in control group with $p < .001$). The mean number of daily regurgitation episodes reduced from 7.4 to 2.6 in test group and 7.5 to 5.3 in control groups at week 0 and week 4 ($p < .0001$) [34].

A double-blind RCT was conducted by Garofoli F, et al., they examine the effect of the *L. reuteri* DSM 17938 in infantile regurgitation with GER. The breastfed full-term 40 infants were randomly distributed to 20 infants received identical placebo and 20 infants received orally *L. reuteri* DSM 17938, 5 drops/daily (100 Million), for 4 weeks. The infants received orally *L. reuteri* DSM 17938 showed significant reduction in regurgitation rates at the completion of treatment ($p= .02$). Thus, initial administration of *L. reuteri* DSM 17938 controls regurgitation events in infants during their first 30 days of life [35].

Another double-blind RCT was initiated on 34 infants by Indrio F, et al., showed that 19 infants on *L. reuteri* DSM 17938 group when compared with 15 infants placebo group showed significant reduction in the sum of daily regurgitation events at day 30 in formula-fed infants ($p < .001$). The significant reduced median fasting gastric area and increased gastric emptying rate in infants with regurgitation as compared with the placebo group at the completion of the intervention phase [36].

The large multi-centric RCT was performed by Indrio F, et al., to evaluate the efficiency of *L. reuteri* DSM 17938 in Functional Gastrointestinal Disorders (FGIDs). In this study, 554 healthy breastfed or formula-fed term-born infants (aged <1 week) were randomly allocated to receive *L. reuteri* DSM 17938 or placebo for 90 days. There was significant decrease in crying time at 30 days (96 vs. 45 min/day; $p < .01$) in *L. reuteri* DSM 17938 group at 90 days (71 vs. 38 min/day; $p < .01$), in comparison to placebo group. The episodes of daily regurgitation were also significantly reduced at day 90 (4.6 vs. 2.9; $p < .01$) and increased the number of daily evacuations at day 30 (2.8 vs. 4.01; $p < .01$) and at day 90 (3.6 vs. 4.2; $p < .01$). Results of this study validates the prophylactic use of *L. reuteri* DSM 17938 in the prevention of infantile colic, regurgitation and functional constipation [37].

Papagaroufalis K, et al, conducted a randomized double-blind trial to evaluate D-Lactic Acid production in healthy 44 infants fed with *L. reuteri* containing formula and 44 infants in control group. The urine d-lactate concentration was primary outcome measured at 7, 14, and 28 day of visits. The urine D-lactate concentration at the 112-day visit was secondary outcomes and other outcomes were urine l-lactate and total (l+d) lactate concentrations, and the ratio of d- to l-lactate at the 7, 14, and 28 day visits; blood acid excess and pH. D-Lactic acid concentration was below non-inferiority margin at 28 days. Regurgitation episodes were significantly fewer in the *L. reuteri* group. The probiotic group had significant lower frequency of hard stools and higher percentage of soft stools [38].

Indrio F, et al, investigated the effect of dietary supplements with probiotic on feeding tolerance gastrointestinal motility in healthy preterm infants in double blinded manner. Thirty infants were included in the study where 10 were breast fed and 10 infants received formula + *L. reuteri* and 10 infants received formula + placebo. The infants receiving *L. reuteri* showed decrease in regurgitation, mean daily crying time, increase gastric emptying rate [39].

CONCLUSION

The available studies on conventional therapies like the use of PPI, prokinetic agents, anti-regurgitation formula and body positioning of infants have a limitation in reducing regurgitation episodes. The conventional therapies had few adverse effects, and some were life threatening.

In the case of L. reuteri DSM 17938 given as drops is a safe probiotic preparation, which can reduce daily reflux, enhances gastric motility, helps to increase body weight, promotes overall growth in infants with gastroesophageal reflux. The parents and caregiver's anxiety and stress related to infant's GER cannot be underestimated hence probiotic L. reuteri DSM 17938 can be a good addition or alternative to current modalities in management of GER. Further research with good quality RCTs are necessary to confirm the benefits.

CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with

respect to the research, authorship, and/or publication of this review article.

AUTHOR CONTRIBUTION'S

The authors Dr. Pramod Prabhakar Jog and Dr. Rahul V Shinde reviewed the manuscript.

FUNDING

The author(s) did not received financial support for the review by Dr. Reddy's Laboratories Ltd. The article processing charges are funded by Dr Reddy's Laboratories Ltd.

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