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A THERAPEUTIC APPROACH FOR THE MANAGEMENT OF GASTROESOPHAGEAL REFLUX DISEASE IN INFANTS

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Abstract: Regurgitation of stomach contents into esophagus is known as gastro-esophageal reflux disease (GERD). Infants are more prone to GERD due to frequent vomiting and regurgitation. Overfeeding with carelessness toward the infant diet is common cause of GERD prevalence in infants. The present review focused on the various pharmacological and non-pharmacological approaches used in the current context to treat GERD in infants. Non-pharmacological method is safe over pharmacological method for treating GERD in infants. Non pharmacological methods include infants positioning, gastric clearance, proper feeding volume and frequency, removing obesity, thickening agents prevents disease progression and decrease reflux disease by preventing infant's exposure to certain risk factor of GERD. Maintaining gastric clearance by using thickening agents of standard quality of cereals, starch and xanthan guar gum, carob bean and soybean polysaccharides improve the digestion of infants but also reduce the GERD progression and enhance nutritional value of infants' feeds. Pharmacological method includes giving medication that reduce the acidity of stomach but also treat the GERD in infants. Several medication antacids, alginates, probiotics, Histamine 2 receptor antagonists, proton pomp inhibitors are given to infants to treat GERD. PPIs are first choice of drugs given to GERD patients as compared to histamine 2 receptor antagonists and prokinetic agents. Antacid and alginate protect oesophagus by reducing acidity and increasing viscosity in stomach. Proton pump inhibitors and histamine 2 receptor antagonists reduce acid secretion by inhibiting the function of receptor underlying the stomach. Prokinetic agents increase motility of stomach and reduce

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obesity. Medication is given according to age, weight, and severity of GERD in infants. Choice of medication with proper dosage form is important for effective therapy. Nissen fundoplication, Linx procedure, Roux-en-Y gastric bypass are effective surgical methods. In Surgical procedure Nissen fundoplication have highest success rate to treat GERD Surgery reduces the long term medical therapy.
Keywords: Obesity, Gastroesophageal reflux disease, Non-pharmacological methods, Pharmacological methods, Regurgitation,

摘要：胃内容物反流到食道被称为胃食管反流病（GERD）。由于频繁的呕吐和反流，婴儿更容易患上胃食管反流病。对婴儿饮食粗心大意而过度喂养是婴儿 GERD 流行的常见原因。本综述重点关注当前背景下用于治疗婴儿 GERD 的各种药理学和非药理学方法。在治疗婴儿 GERD 时，非药物方法比药物方法更安全。非药物方法包括婴儿体位、胃清除、适当的喂食量和频率、消除肥胖、增稠剂通过防止婴儿暴露于某些 GERD 危险因素来防止疾病进展和减少反流病。通过使用标准质量的谷物增稠剂、淀粉和黄原胶瓜尔胶、角豆和大豆多糖来保持胃部清除率，可以改善婴儿的消化，同时也可以减少 GERD 的进展并提高婴儿饲料的营养价值。药理学方法包括给予降低胃酸的药物，但也治疗婴儿的 GERD。几种药物抗酸剂、藻酸盐、益生菌、组胺 2 受体拮抗剂、质子抑制剂被给予婴儿以治疗 GERD。与组胺 2 受体拮抗剂和促动力剂相比，PPI 是给予 GERD 患者的首选药物。抗酸剂和藻酸盐通过降低胃中的酸度和增加粘度来保护食道。质子泵抑制剂和组胺 2 受体拮抗剂通过抑制胃下受体的功能来减少胃酸分泌。促动力剂增加胃的动力并减少肥胖。根据婴儿 GERD 的年龄、体重和严重程度给予药物治疗。选择合适剂型的药物对于有效治疗很重要。 Nissen 胃底折叠术、Linx 手术、Roux-en-Y 胃旁路术是有效的手术方法。在外科手术中，尼森胃底折叠术治疗 GERD 的成功率最高。手术减少了长期的药物治疗。
关键词：肥胖，胃食管反流病，非药理学方法，药理学方法，反流，

1. Introduction

GERD is a digestive disorder in which the gastric content backflow to the oesophagus [1]. Regurgitation of gastric reflux is the main cause of GERD in infants. Infant's regurgitation is highest during early six months. In infants mucus membrane is less resistant and valve which prevents regurgitation of gastric content is highly sensitive and not too resistant. Increase in pressure inside the stomach cause the valve to open. Opening of valve make a way for gastric content to regurgitate and damage the oesophagus.

Infants during early developmental stage may have aero vascular, cardiovascular and

respiratory disease it's is challenging to confirm whether the symptoms are due to gastric disorder or any other disease. GERD cause troublesome to infants and if not treated in early stage its severity increases continuously and cause esophagitis, Barrette's esophagus or even esophageal adenocarcinoma which is last stage of GERD [2]. Acute GERD have minor symptoms and can be controlled by taking certain preventing measure. GERD if not controlled by giving certain medication take chronic form. Medication with primary health care is necessary for proper treatment. Infant's treatment performed by various non-pharmacological and pharmacological treatments this include proper sitting, bending, laying position and giving antacid, prokinetic agents and other over the counter medication[3, 4].

North American Society for pediatric gastroenterology, hepatology, and nutrition (NASPGHN) and European Society for pediatric gastroenterology, hepatology, and nutrition (ESPGHN) have given pediatric gastroesophageal reflux clinical guidelines for the treatment of GERD [5]. NASPGHN and ESPGHN have given guideline that infants with regurgitation, vomiting with other symptoms of bilious vomiting, gastrointestinal bleeding, hematemesis, hematochezia, consistent forceful vomiting, onset of vomiting after 6 months of life, failure to thrive diarrhea, constipation, fever, lethargy, hepato-splenomegaly, bulging fontanelle, Macro-/microcephaly seizures, abdominal tenderness or distension are suspected to possess GERD[6, 7].

2. Epidemiology of GERD in Infants

Epidemiology of GERD in infants is based on various factors such as prevalence rates, clinical manifestation, selection of population, nutrition, over the counter treatment, different type of diagnostic and treatment method which are taken into consideration in overfeeding infants [8]. Overfeeding is common cause of increase in epidemiology of GERD infants. It is quite difficult to exact quantify the amount of milk which should be given to breast feed infants. Less feeding make infants weak and overfeeding lead to regurgitation. Epidemiological data of GERD shows that GERD prevalence which is approximately 50% in infants of less than 2 months, 60 to 70% in 3 to 4 months and 5% in infants of 12 months. GERD is higher during early four to five month of infants age but as the age progresses to one year it resolve completely by taking proper treatment methods up to 95% of GERD infants are treated completely [9, 10]. According to consensus across worldwide GERD are spread across the 30% of the total population. Regurgitation is common in infants due to large volume of liquid intake. Infants have limited capacity i.e. 10 ml liquid intake if total water, milk and other meal contents exceed the limit regurgitation and vomiting are possible. Gastroesophageal reflux (GER) epidemiology is higher in monozygotic twin as compared to dizygotic twin. GERD prevalence rate is double in male then female. GERD is less in breast milk feeding infants, infants of cow milk allergy or infants taking marketed milk. Reduction in the prevalence of breast milk feeding infants is because of more rapid gastric emptying as compared to standard milk and other nutritive, immunological substance which are useful for infant's maturity and proper development [11].

3. Non- Pharmacological Methods of Treating GERD in Infants

Non pharmacological method of treating GERD include treating the disease by maintaining primary health care of infants by taking care suitable position of infants, maintaining gastric clearance, proper feeding volume and frequency, proper use of thickening agents, massage therapy, parental smoking parental education, guidance and support, reducing obesity. Non pharmacological therapy is safe, effective with no serious side effect [12, 13].

3.1 Infants positioning in GERD

Position of infants is important in GERD. Infants can't stand and sit by itself they ultimately reach in unsuitable position and increase the pressure of stomach. Valve of infants are not so resistance to this increase in stomach pressure. Increase pressure of stomach open valve and cause infants to regurgitate. Left lateral position of infants with 20º head out elevation is suitable to prevent regurgitation [14, 15]. Proper position of infants makes clear way of stomach content down toward the intestine easily if meals is easily digested then there is less chance of regurgitation in GERD infants.

3.2 Gastric clearance in GERD infants

Gastric clearance is composed of chemical and volume clearance. In infants for treating GERD both gastric clearance is in stable state. Volume clearance is stable if there is proper swallowing and peristalsis movement of the oesophagus. Chemical clearance is stable if excessive acid of the stomach is neutralized by saliva or gastric juice present in the stomach [16]. Gastric clearance can be monitored by combined pH-multichannel intraluminal impedance. If GERD infants show changes in gastric clearance level then oral basic solution, mucosal protective agent and other agents can be given to keep gastric clearance in stable state.16 Efficiency of volume clearance of reflux episode is generally assessed and evaluated by distal impedance channel. Chemical clearance is defined by a new parametric index known as post-reflux swallow-induced peristaltic wave (PSPW), PSPW is 50% drop in gastric impedance in comparison to baseline level. PSPW is calculated in 30s. Greater the PSPW count greater the chemical resistance. PSPW index is calculated both for the pH less than 4 and pH more than 4 [17]. If gastric clearance measured at the time when GERD infants is awaked there is increased PSPW index and if GERD infants is sleeping then there is decrease in gastric clearance due to reduction in the frequency of swallowing episodes which decrease volume clearance.

3.3 Maintaining proper feeding volume and frequency

Feeding volume and frequency of feeding vary according to infant's digestive system. In some infants digestive system is more functional and meals easily digested but the cause of GERD in these infants is due to other impairment in digestive system or allergy. Feeding hourly to infant is recommended to GERD infants. Quantity of milk given is based on the age however average volume that should be given to infants is 150 ml/kg/days but the quantity of milk given vary according to the infant condition and disease severity [18].

3.4 Use of thickening agents in meals of GERD infants

Thickeners are used in infant's meals to change the nutritional value of food. Thickeners change the composition of meals of infants. Varieties of

thickeners are available in market. Thickeners of cereals, starch and xanthan guar gum, carob bean and soybean polysaccharides they are always used in standard dose. Certain thickeners if used in high quality may increase the GERD severity [19, 20]. GERD infants are given easily digestible thickeners. Xanthan guar gum, carob bean gum and soybean polysaccharides decrease the intestinal absorption of carbohydrates, fats, calcium, iron, zinc, and copper which decrease the health of infants. Certain thickening agents contain arsenic which exposes infant to some serious disease such as cancer, cardiovascular and respiratory disease. Arsenic limit for infant rice cereals is 100 parts per billion as stated by United States Food and Drug Administration and European commission [21]. Thickeners of cornstarch, carob, bean gum, rice wheat and oat based thickeners affect the micro flora of intestine and reduce the gastro intestinal transit. Thickeners affect the intestinal absorption of various vitamins and minerals along with carbohydrate, Fats and protein. Regurgitation is decreased by taking beans containing thickeners. Overall thickeners are effective up to certain extent as it reduce the GERD [22, 23]. Extensively hydrolyzed protein formulas that are given to infants are used in large manner, improve feeding tolerance, reduce gastrointestinal transit time, increases stool frequency and improve the symptoms of GERD in infants [24].

3.5 Removing obesity in GERD patients

Obesity is risk factor for infants GERD. GERD can be treated by removing obesity in infants. Obesity increases the body mass of infants due to decrease in metabolism of body. Certain factors are responsible for obesity in infants. Factors include change in the enzyme activity of stomach, decrease in motility of stomach. Increase in fatty acid level in infants meals. If food reside in stomach over prolonged time its cause obesity. Obese infants are at risk to other disease due to obesity they not take proper nutritious diet and slowly their body become weak, Infants already have GERD facing difficulty to cope with GERD severe symptoms at this condition if person weak they get easily infected by other disease which effect infants proper maturation and development. If infants maturation is not proper infants always at risk of other diseases Obesity problem in infants could be overcome by taking care of infants feeding routine, quantity of feed, giving infants easily digestible food and low quantity of food in continuous manner. Changing feed composition is one of the important steps to remove obesity in infants. If easily digestible meal is given in adequate amount there is no more obesity problem in infants. If infants have no obesity there is no GERD [25].

3.6 Avoiding parental smoking

Parent smoking is avoided in front of GERD infants. Reflux increase when infants are exposed to certain central nervous system stimulant (CNS). Tobacco product contain nicotine one of the CNS stimulant. They increase cardiovascular, respiratory, digestive motility resulted in oesophagitis in infants. Symptoms can be observed instantly in infants are desaturation, crying, vomiting, and feeding problems [26].

3.7 Parental education, guidance and support

Parental education is important in infant to increase severity of GERD. Care of infant with suitable sleeping, sitting position and proper diet with quality and quantity of food reduce the

GERD up to certain extent. If these care is avoided in infants GERD increase continuously at an accelerated rate. Continuous overfeeding increases the symptoms of GERD [27, 28]. Giving anti-regurgitation formulas decrease overt regurgitation and decrease GERD in infants. Hydrolyzed protein formula is given to GERD infants for removing digestive problem. Hydrolyzed protein formulas are made of cow milk with ingredient that are broken easily. Infants allergic to milk can be given hydrolyzed protein formulas which are easily digestible [29]

4. Pharmacological Methods of Treating GERD in Infants

Pharmacological methods include the use of several class of medication to treat GERD. Several class of medication which is given to GERD infants are antacid, alginate proton pump inhibitors (PPIs), histamine 2 receptor antagonist (H2RAs), Prokinetic agents [30].

4.1 Antacids

Antacid are drugs which decrease the acidity of stomach. Antacid drugs are made of various metal combined with their oxide and hydroxide. They are weak bases after meal 45 mEq/h of hydrochloride acid is secreted in the stomach to neutralize this much amount of acid 156 mEq of antacid is given after one hours give relief to GERD infants for 2 hours. Drugs which come under antacids are aluminum hydroxide, magnesium hydroxide, sodium hydroxide, Calcium carbonate, calcium hydroxide. Antacid are taken in accurate dose overdose of antacids lead to various serious neurological, hypophosphatemia, rickets, aluminum toxicity, osteopenia, neurotoxicity, microcytic anemia. Antacid are taken orally they give instant relief within 5 minute to one hours by decreasing acidity of stomach. Antacids not treat GERD in infants. They give symptomatic relief. If GERD persist over long term then antacid intake is instantly stopped and other medication should be taken to treat the GERD in infants [31]. Antacids change the pharmacokinetic and pharmacological action of other drugs. Antacid decreases solubility of other drugs in infant's stomach. If solubility of drugs is altered the drugs take more time to soluble and this cause decrease in metabolism of medication which delay and reduce the availability of concentration of drugs which is required to perform pharmacological action.

4.2 Alginates

Alginates are polysaccharide made of insoluble salts of alginic acids contain mainly magnesium, sodium and manintol. Alginate is mucoprotective agent protect the mucus membrane of the oesophagus from strong acid present in oesophagus. Sodium alginates are associated with bezoar formation, Sodium alginates should be given with caution in infants i) which are born preterm, ii) suffering renal impairment, iii) with congestive cardiac failure, iv) with diarrhea and vomiting with risk of dehydration Alginates make the gastric content viscous. Alginate interact with acidic content of the stomach and form a gel like substance and the foamy gel that look like a raft create a pH neutral barrier between acidic content of stomach and inner lining of oesophagus. This barrier protects the inner lining of infants. Alginates have immediate action within one hour. It has main advantage that it also useful in non-esophageal GERD infants [32, 33]

4.3 Probiotics

Probiotic agents are also known as prokinetic agents they increase the movement of digestive system of infants. Prokinetic agents include all agents which act on the receptor and increase the gastric motility, for e.g. cholinergic agonists, dopamine antagonists, serotonergic agonists, and macrolide and ghrelin agonist.

Cholinergic agonist has central and peripheral action. Cholinergic agonist reduces GERD in infants by decreasing lower esophageal sphincter. It efficacy is limited and possess side effect which can't be minimized by using other medication. Cardiac arrhythmias, sudden death, bronchospasm, diarrhea, extensive sweating and other symptoms are associated with the use of cholinergic agonist [34, 35]. Dopamine antagonists that are used in GERD infants are metoclopramide, domperidone, cisapride, tegaserod. Dopamine antagonists have prokinetic effect but many side effects are also associated with these drugs. Some of them possess antiemetic effect by acting on 5HT4 and 5HT3 receptors. Adverse effect of dopamine antagonists are dysrhythmia, respiratory distress and even cardiac arrest, neuroleptic malignant syndrome and tardive dyskinesia. Dopamines antagonists at high dose will have prolonged duration of action with benefit outweigh the risk factor they are given to infants more than one year age [36]. Serotonergic agents contain drugs acting of 5HT receptor. Drugs include cisapride, mosapride, pruclapride, and serteronergic agents increase release of acetylcholine from neurons. It has prokinetic action in GERD infants but fatal cardiac arrhythmias are associated with some GERD infants [37, 38]

Macrolide include the erythromycin act as motilin receptor agonist. One of the antibiotic lactobacinate is used at a dose of 3mg/kg in infants however dose is variable according to severity of reflux disease. It is used only for short term and the drugs are usually not taken due to various risk assosciated with the use of these drugs. Azithromycin is another better drug which accelerates gastric emptying and stimulates small intestinal motility [39, 40]. Ghrelin agonists are endogenous analogue of growth hormone. ulimorelin, relamorelin are used in GERD infants to increase gastrointestinal motility. Relamorelin have better effect than ulimorelin. Ghrelin agonists are not used as much in infants due to low potential to treat GERD in infants [41].

4.4 Role of H2-receptor antagonists (H2RAs) and proton pomp inhibitors (PPIs) in the treatment of GERD in infants

PPI and H2RA are first choice of drug in infant for erosive oesophagitis and non- erosive oesophagitis. PPIs are 95% bound to plasma protein. They have short half-life of one hour. PPIs are metabolize by CYP2C19 and CYP3A4 to inactive metabolite and excreted in faces. Activity of these CYP systems is low in infants and it takes four to six month to reach it activity to maximum level in infants. In certain studies when irritable infants underwent a randomized, double-blind, placebo-controlled, crossover trial with omeprazole lower reflux symptom observed [42, 43]. In other studies multicenter randomized clinical trials, GER and antacid medications in double-blind, placebo-controlled trial with lansoprazole in infants who experienced crying, fussing, or irritability within 1 h after feeding found no difference in efficacy among lansoprazole and placebo as measured by symptom quantity and duration [44, 45]. Esomeprazole more recent study as effective drug in reducing esophageal acid exposure and

the number of acid reflux events [46]. Esomeprazole is used in infants for healing of erosive esophagitis in younger than 1 year of age and as early as 1 month. Rabeprazole is another PPIs used in infants effectively. PPIs are potent medication treat GERD completely. Dose of PPIs can be varying according to severity of disease. Vomiting nausea, dizziness are some of the side effect associated with short term intake of PPIs but if use over long term it's have serious effect such as pneumonia, hypomagnesaemia, Clostridium difficile diarrhea, vitamin B12 deficiency, kidney disease and dementia [47, 48]. PPIs change the micro-biome of the mouth lungs and guts. In a similar manner PPIs increases the small bowel bacterial growth with pain, diarrhea, and nutrient mal-absorption. Other drugs revaprazan, vonoprazan, and fexuprazan, Tegoprazan are potassium- competitive acid blockers, which have no PPIs drawback and other limitations.

H2RAs are acid-suppressing agents frequently used in various gastric and peptic diseases, including duodenal, gastric ulcers, GERD and heartburn. H2RAs include drugs cimetidine, ranitidine, and famotidine [49]. Mode of action of H2RAs is they act at basolateral surface of gastric parietal cells thereby interferes with gastric acid production and secretion mechanism. Ranitidine is effective drug but it side effect are seen such as diarrhea, fatigue, dizziness. It has some carcinogenic effect due to presence of nitrosamine [50] Cimetidine is not given in infants as it interacts with cytochrome P450 and cause serious side effects. Other H2RA, nizatdine, famotidine are also not prescribed with cimetidine to GERD infants [51, 52].

In brief PPI s is effective drug than H2RA. It should only be taken when non pharmacological treatment fails in GERD in infants. Proper dose and dosage regimen is important in infants to treat the GERD with minimum side effects [53, 54].

5. Surgical treatment of GERD in infants

Nissen fundoplication, Linx procedure, Roux-en-Y gastric bypass are different surgical methods performed to treat GERD in infants [55, 56] Surgery is performed only when all other medication fails. Complete checkup reports of infants are evaluated completely and then decision is taken whether surgery is performed or not. Laparoscopic Nissen fundoplication is best surgical treatment for the GERD. Success rate of this technique is 86%.Pre and post-surgical complications are always in surgical therapy. Complete investigation of the oesophagus before doing surgery is performed. Maximum mortality of 0 to 29% found in surgical treatment. Cardiac, neurological or respiratory disorders are cause of mortality in the infants undergoing surgical therapy. In Linx procedure laparoscopic insertion magnetic beads around the lower esophageal sphincter is wrapped completely, which make free passage of food and other liquid substance. It is closed after meals is passed through and then its closes to prevent reflux of acid [57, 58]. Linx procedure treats the GERD and provides symptomatic relief to infants and reduces symptom scores. Roux-en-Y gastric bypass is performed in obese GERD infants. It is performed laparoscopically. In surgery stomach upper portion is separated from the lower portion make a gastric bypass through it. New stomach that's formed gives us fullness of eating by the intake of intake of more quantity of food. Roux-

en-Y gastric bypass reduce obesity which is major cause of GERD in infants [59, 60].

6. Conclusion

Infants need extra care and vigilance than others as they can't express themselves. They are prone to several gastric diseases. Proper care, education and parental guidance can prevent GERD progression. GERD can be prevented by paying adequate heed towards their meal, posture of sleeping, timely medical checkup and parental education. If the symptoms of GERD are seen in any infant it can be treated very easily by preventive measures. In case preventive measures fail to treat GERD then medication will be required. Medication starts with use of alginates, prokinetic agents, antacids, PPIs and H2RA. If medications are not effective then surgery is required after proper checkup of infant. Nissen fundoplication, linx procedure, Roux-en-Y gastric bypass are effective surgical method to treat GERD in infants. Surgery improves infant health and treats GERD to great extent.

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Conflict of Interest

The authors declare no conflict of interest.

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