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REVIEW

Comparative Analysis of Pharmacological Treatments and Lifestyle Modifications for Managing Gastroesophageal Reflux Disease in Infants: A Literature Review

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Abstract

Gastroesophageal reflux disease (GERD) is a common condition in infants, causing vomiting, irritability, and feeding difficulties. Though typically mild and self-limiting, severe cases may result in complications such as esophagitis, failure to thrive, or recurrent aspiration pneumonia. This review highlights a tiered approach to management, emphasizing non-pharmacological methods such as feeding adjustments, and thickened feeds as first-line treatments. These strategies are effective for mild to moderate cases, reducing unnecessary medication risks. Pharmacologic interventions, primarily proton pump inhibitors and histamine-2 receptor antagonists, are reserved for severe cases, such as erosive esophagitis or persistent respiratory symptoms, where non-pharmacological approaches have failed. While medications promote mucosal healing, their efficacy for symptoms like irritability or vomiting in non-severe cases is mixed, raising concerns about overuse. Adverse effects include increased infection risks, gut microbiota changes, and nutrient malabsorption. Future research should refine diagnostic criteria and develop evidence-based guidelines to prevent overtreatment.

Key words: gastroesophageal reflux disease; infants; feeding behavior; dietary therapy; proton pump inhibitors

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Introduction

Gastroesophageal reflux disease (GERD) is a prevalent condition in infants, affecting 4 out of 10 infants (NICE, 2015), marked by the regurgitation of stomach contents into the esophagus, causing symptoms such as vomiting, irritability, and feeding difficulties (Carroll et al, 2002; Tighe et al, 2023). The main mechanism of GERD is due to relaxation of the lower esophageal sphincter (LES). While GERD is often mild and typically resolves within the first year of life, it can cause significant discomfort and, in severe cases, lead to complications like esophagitis, respiratory issues, and poor weight gain. These challenges can significantly affect an infant's overall quality of life, resulting in sleep disturbances, feeding difficulties, and heightened parental anxiety (Vandenplas et al, 2009). Both non-pharmacological and pharmaceutical approaches are used to treat GERD in newborns, but treatment choices are debatable since there are no established protocols, questions about the effectiveness and safety of drugs, and difficulties putting lifestyle modifications

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into practice (Sintusek et al, 2023). This review aims to compare current treatment approaches of GERD, highlighting their effectiveness, limitations and challenges, helping to identify gaps in current treatment as well as highlighting the need for more effective treatment plans for infants with GERD.

Methods

To investigate the relationship between GERD and treatment practices in infants, various information sources were utilized. Websites, research papers, review articles, and reports were identified through a combined approach using Google search and academic databases like the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/) and Google Scholar (https://scholar.google.com/). The search used keywords such as "Gastroesophageal reflux disease", "Infants", "Dietary Therapy", "Feeding Behavior", and "Proton pump inhibitors" to ensure comprehensive coverage of relevant literature on both pharmacologic and non-pharmacologic treatment approaches, as well as efficacy and safety considerations.

The literature was selected based on criteria such as inclusion of one or more of the specified keywords, relevance to the research question, and publication within the past 30 years. Many articles were excluded for not meeting these standards.

When reviewing each article, reading each piece thoroughly and understanding the key concepts were top priorities. Relevant data, including the author, publication year and relevant findings, were extracted from the literature and methodically arranged. These findings were analyzed to identify themes and gaps in current literature, and the implications, limitations and potential directions for future research.

Approaches to Treating Gastroesophageal Reflux Disease

Treatment for infant GERD typically follows a tiered approach, beginning with non-pharmacological methods and progressing to pharmacological options only when necessary. Non-pharmacological strategies, such as modifying feeding schedules and using thickened feeds, are the initial treatments of choice. Studies indicate that thickened feeds, such as formula mixed with rice cereal, can significantly reduce regurgitation episodes in infants (Sintusek et al, 2023). For infants experiencing severe symptoms or complications like esophagitis, pharmacological treatments, including proton pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs), may be considered. While PPIs like omeprazole are more effective than H2RAs in reducing acid production and esophageal inflammation (Dermyshi et al, 2018), their long-term use in infants is limited due to potential risks such as malabsorption and increased susceptibility to infections.

Clinical guidelines, such as those from the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), emphasize non-pharmacological interventions as the primary approach, with medications reserved for persistent or severe cases (Vandenplas et al, 2009).

Stepwise Management Approach

The management of infant GERD involves a structured, step-by-step strategy. Initially, symptoms such as fussiness, reluctance to feed, and frequent non-projectile regurgitation are evaluated. If serious red flags like hematemesis or abdominal distention are absent, the next step is to assess for overfeeding. Recommendations may include reducing feed volumes or offering smaller, more frequent feeds. The use of thickening agents, such as carob bean gum, may also be introduced at this stage to help alleviate symptoms.

If symptoms persist, alginate therapy can be considered, with symptom resolution monitored over 1–2 weeks. For infants whose symptoms remain unresolved, a trial of PPIs or H2RAs may be warranted, particularly in cases involving regurgitation, distress, or faltering growth. Medication effectiveness should be reassessed after four weeks, and if symptoms improve, gradual weaning and discontinuation of the medication should follow.

For cases where symptoms persist despite these measures, referral to a pediatric gastroenterologist is advised. Further diagnostic evaluations may be required to identify underlying causes, and advanced interventions or surgical options may be explored as necessary (NICE, 2015).

The Role of Non-Pharmacological Treatment in Gastroesophageal Reflux Disease

The Journal of Pediatric Gastroenterology and Nutrition emphasizes non-pharmacological approaches as first-line treatments for GERD in children. These approaches include dietary modifications, such as avoiding overfeeding and eliminating food triggers like chocolate and spicy foods. Elevating the head of the bed and keeping infants upright after meals can help reduce reflux symptoms. For mild cases, parental education and lifestyle adjustments are crucial, potentially reducing the need for medication or surgical intervention (Carroll et al, 2002). Careful body positioning after meals is promoted since studies have noted that while flat prone and left-side down positions are beneficial when infants are awake (Baird et al, 2015). However, changes in an infant's position, such as feeding them while seated upright in a chair, have been shown to exacerbate symptoms of GERD. A randomized controlled trial by Orenstein et al (1983) measured reflux using distal esophagus pH monitoring and found that infants seated upright at a 60-degree angle experienced prolonged exposure to refluxed material compared to those placed in a prone position.

Orenstein (1988) also investigated the impact of pacifier use in infants positioned either upright in a chair or lying prone. The findings indicated that pacifier use while seated upright increased the number of reflux episodes, whereas pacifier use in the prone position reduced the overall number of episodes. However, it is important to note that the general risks associated with the prone position, particularly its link to sudden infant death syndrome (SIDS), outweigh its potential benefits for reducing reflux. In line with this, the NICE (2015) guidelines and Baird et al (2015)

findings emphasize that positional changes should not be relied upon to alleviate GERD symptoms, as they may inadvertently increase the risk of SIDS.

The use of thickened feeds in managing GERD has shown mixed results. For example, two studies found that thickened feeds were effective in reducing cough and the height of reflux in the esophagus, but they did not significantly affect the frequency or other characteristics of reflux episodes. Additionally, thickened feeds have been associated with side effects such as weight gain, constipation, dysmotility, and necrotizing enterocolitis (Beal et al, 2012; Njeh et al, 2024). Njeh et al (2024) also observed that thickened feeds prolonged bolus clearance from the esophagus, potentially increasing esophageal damage due to extended exposure to refluxed material. These findings collectively suggest that neither positional changes nor thickened feeds are consistently effective or without risk in managing GERD symptoms in infants.

An advantage of non-pharmacological treatments is their effect on both acid and non-acidic GERD, whereas pharmacological therapies often target only acidic types (Corvaglia et al, 2013). Acid suppressive therapies, such as PPIs, have been linked to an increased risk of neonatal infections and even death in very low birth weight infants. In children, PPIs may increase the risk of community-acquired pneumonia and gastroenteritis (Baird et al, 2015). Conservative methods tend to have fewer side effects, making medication avoidable in many infants since physiological GERD often resolves by the first year. However, while medications typically provide better long-term symptom relief, infants with neurodevelopmental disabilities, who may experience both dysphagia and GERD, may require pharmacological treatment when non-pharmacological therapy is insufficient. Additionally, according to research suggests that thickeners like xanthan gum may increase the risk of necrotizing enterocolitis in neonates (Beal et al, 2012). Although adding 1 tablespoon of rice cereal per oz of formula can lead to excess weight gain, it may not effectively reduce esophageal acid exposure. Careful body positioning after meals is promoted since studies have noted that while flat prone and left-side down positions are beneficial when infants are awake, they should always sleep in the supine position to prevent sudden infant death syndrome (Baird et al, 2015).

The Role of Proton Pump Inhibitor in Gastroesophageal Reflux Disease

There is mixed evidence that supports the use of PPIs to treat infantile GERD like symptoms. In a study involving 30 infants aged 3 to 12 months with confirmed GERD, omeprazole, a PPI, significantly reduced the reflux index, defined as the percentage of time esophageal pH remained below 4 during a 24-hour pH monitoring period. Infants receiving omeprazole demonstrated an average reduction in reflux index of 8.9%, compared to a 1.9% decrease in those given a placebo ($p = 0.001$) (Moore et al, 2003). This result suggests that omeprazole can effectively reduce acid exposure in the esophagus of infants with GERD, highlighting its therapeutic potential for this age group.

Despite the apparent effectiveness and long-standing perception of PPIs as low-risk and well-tolerated medications, recent studies in adults have raised concerns about their safety profile. These adult studies have identified potential risks and adverse effects associated with long-term PPI use, prompting a reevaluation of their risk-benefit balance, especially in vulnerable populations like infants (Smith et al, 2013).

A recent systematic review that included five placebo-controlled studies involving infants aged 34 weeks postmenstrual to 12 months concluded that PPIs are not effective in reducing common symptoms of GERD in infants, specifically feeding-related crying and irritability. Despite PPI treatment, symptoms such as irritability did not significantly improve, indicating the limited efficacy of these medications in addressing GERD-related discomfort in infants (van der Pol et al, 2011).

Safety concerns regarding PPI use in infants under one year of age are significant, as data on appropriate dosage and potential risks are limited. In a study involving 186 children aged 4 to 36 months, monitored over a four-month period, those who received gastric acid inhibitors, including PPIs, demonstrated higher incidences of adverse effects compared to those in the control group. Specifically, there was a substantial increase in acute gastroenteritis episodes (47% in the PPI group vs. 19% in controls, $p = 0.001$) and pneumonia cases (12% in the PPI group vs. 2% in controls, $p = 0.03$), raising red flags about the potential for increased susceptibility to infections among infants on acid suppression therapy (Canani et al, 2006).

Current guidelines for treating GERD in infants younger than one year of age advocate a conservative approach. Experts recommend that PPIs be considered only after referral to a pediatric gastroenterologist and after non-pharmacological interventions have been attempted without success. Initial, recommended strategies include thickening feeds and avoiding overfeeding, followed by second-line approaches like cow's milk elimination and allergy consultation. These steps address common factors that may contribute to GERD symptoms without exposing infants to medication-related risks (Rosen et al, 2018).

Furthermore, infantile reflux is often a normal, physiologic occurrence that tends to resolve on its own between the ages of 6 and 12 months. In most cases, this natural maturation process reduces reflux episodes, suggesting that medication may not be necessary for many infants who exhibit mild symptoms (Rosen et al, 2018). This trend supports the concept that infant irritability may naturally improve as infants age, irrespective of PPI intervention. Consequently, this finding suggests that time, rather than pharmacological intervention, may play a more substantial role in alleviating GERD-like symptoms in young infants (Moore et al, 2003).

The use of H2RAs for treating GERD in infants has been extensively evaluated, with mixed findings. A review of 27 studies assessing the efficacy and safety of PPIs and H2RAs in neonates and infants with GERD highlights that while both classes of medication demonstrate positive pharmacodynamic effects such as increasing gastric pH, reducing the reflux index, and decreasing acidic reflux events, they show limited evidence of clinical benefit for key GERD symptoms like irri-

tability, feeding tolerance, and weight gain. Although these medications are generally well tolerated, large retrospective studies have raised safety concerns, including associations with increased incidences of allergies, anaphylaxis, necrotizing enterocolitis, nosocomial infections, and lower respiratory tract infections (Tan et al, 2023).

A study conducted in Iran revealed that H2RAs, in particular, have shown efficacy in reducing GERD symptoms but have certain limitations. They have a slower onset of action and require higher doses to achieve sufficient acid suppression compared to PPIs. However, H2RAs are often better tolerated in infants due to their availability in syrup form and their lower cost, which may make them a more viable option in resource-limited settings (Azizollahi and Rafeey, 2016). This conclusion, however, is context-dependent, as this study conducted in Iran by Azizollahi and Rafeey (2016), highlights that regional medication formulations and prices may have influenced their findings, limiting the generalizability of these results to other parts of the world.

The efficacy of PPIs has been found to be comparable to H2RAs in managing GERD symptoms in infants. A randomized controlled trial by Azizollahi and Rafeey (2016), revealed no statistically significant differences between ranitidine (an H2RA) and omeprazole (a PPI) in their ability to alleviate GERD symptoms. However, evidence suggests that PPIs are superior to H2RAs in treating certain complications associated with GERD, such as esophagitis. A meta-analysis conducted by Wang et al (2005), demonstrated that PPIs were significantly more effective than H2RAs in treating esophagitis across all severity grades. The success rates for esophagitis resolution with PPIs compared to H2RAs were 100% vs. 64% for grade 1, 93.3% vs. 55.5% for grade 2, and 59.6% vs. 17.6% for grades 3 and 4. This includes cases where patients showed resistance to H2RA treatment (Wang et al, 2005).

These findings indicate that while PPIs and H2RAs show similar efficacy in alleviating general GERD symptoms in infants, PPIs are significantly more effective in reducing complications such as esophagitis, making them a preferred treatment option in such cases.

A study utilizing esophageal multichannel intraluminal impedance monitoring paired with pHmetry found that, although caregivers reported over 4000 bouts of reflux-like symptoms in newborns, only 9% were associated with acidic reflux events. This finding indicates that many reported symptoms may not be linked to true acidic reflux, highlighting the potential for overdiagnosis and overtreatment of GERD in infants. Taken together, these data support the need for caution in prescribing PPIs to infants and emphasize the importance of carefully considering alternative, non-pharmacological strategies for managing GERD symptoms in this age group (Garza et al, 2011).

Special Population

GERD is significantly more common in children with neurodevelopmental impairments, such as cerebral palsy, mitochondrial disease, and epilepsy. The primary

underlying mechanism in this population is thought to be the absence of LES tone. However, due to the nonspecific symptoms, detection can be challenging. As a result, GERD in these children is often diagnosed late, leading to severe complications, including esophagitis and aspiration pneumonia (Kim et al, 2017).

Children with neurological impairments also tend to experience more severe GERD symptoms and complications, for example, erosive esophagitis affects 30–50% of children with neurodevelopmental disabilities, whereas it occurs in only 5% of children without such impairments (Esposito et al, 2015). Moreover, conservative management, such as feeding adjustments and positional changes, is often insufficient for these children. Consequently, they frequently require long-term medication or surgical interventions (Dewan et al, 2022).

Despite the high prevalence and severity of GERD in this vulnerable population, there is a significant lack of comprehensive research and evidence-based guidelines for treatment. Addressing these gaps through further investigation is essential to develop tailored, effective treatment strategies that meet the unique needs of children with neurodevelopmental disabilities.

Conclusion

Managing infantile GERD requires a comprehensive and tiered approach that prioritizes non-pharmacological interventions before escalating to pharmacological treatments. While GERD is often mild and self-limiting, severe cases can significantly impact an infant's quality of life and require careful assessment and intervention. Non-pharmacological strategies, including feeding adjustments and thickened feeds, are effective first line treatments for most infants and help minimize unnecessary medication exposure.

Pharmacologic therapies, such as PPIs or H2RAs, should be reserved for cases unresponsive to conservative measures or those involving complications like esophagitis, poor growth or neurodevelopmental patients. However, concerns about the safety and efficacy of acid suppressive medications underscore the importance of cautious use, particularly in infants. For infants with persistent symptoms despite tiered management, referral to a specialist is essential to explore underlying causes and potential interventional options.

This review highlights the need for continued research to refine diagnostic criteria, improve treatment protocols, and balance the benefits and risks of pharmacological interventions in managing GERD. Tailored, evidence-based strategies remain critical for optimizing outcomes and minimizing overtreatment in this vulnerable population.

Key Points

- GERD in infants causes vomiting, irritability, and feeding issues; severe cases can lead to esophagitis and poor growth.
- Start with non-pharmacologic methods (feeding changes and thickeners), using medications only for severe cases.
- PPIs and H2RAs may reduce acid but show mixed symptom relief and increase infection risks, so caution is needed.
- GERD symptoms often resolve after the age of one, making non-pharmacologic methods sufficient for many infants.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

YM, YJR and TJ designed the research study. YM and YJR analyzed the data. TJ drafted the manuscript. All authors contributed to important editorial changes of important content in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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