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# Gastroesophageal Reflux Disease In Neonates And Infants: A Systematic Review To Identify Best Practice For Treatment

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GASTROESOPHAGEAL REFLUX DISEASE IN NEONATES AND INFANTS:  
A SYSTEMATIC REVIEW TO IDENTIFY  
BEST PRACTICE FOR TREATMENT

by

Kristen M. McKinnon

A Master's Thesis Presented in Partial Fulfillment  
Of the Requirements for the Degree  
Master of Science, Health Service Administration

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I have **READ AND ACCEPTED**

the Master's Thesis by:

Kristen M. McKinnon

Gastroesophageal Reflux Disease in Neonates and Infants:  
A Systematic Review to Identify  
Best Practice for Treatment

Submitted in partial fulfillment of  
requirements for the  
Master of Science in Health Services Administration  
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Primary Research Advisor:

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### *Abstract*

Many infants have some form of gastroesophageal reflux (GER) characterized by occasional spitting up with burps. Symptomatic reflux called gastroesophageal reflux disease (GERD) affects infants and causes a variety of symptoms and observable events. The diagnosis of GER or GERD appears to be increasing in the infant population including healthy newborns and those infants hospitalized for a variety of reasons. The purpose of this systematic review is to identify evidence-based practice guidelines for the treatment of GERD, including pharmacologic and non-pharmacologic interventions in the neonatal/infant population. The results of this study show that conservative therapies should be used initially in the treatment of GERD. If conservative therapies are unsuccessful, interventions including feedings can be used prior to the addition of pharmaceutical therapies.

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## Chapter 1. Introduction

### *Introduction to the Problem*

Gastroesophageal reflux (GER) refers to the presence of gastric contents in the esophagus proximal to the stomach (Mohan & Soni, 2002). Symptomatic reflux called gastroesophageal reflux disease (GERD) includes infants who have a variety of symptoms and observable events including vomiting more than two times per day, desaturations, arching, drooling, recurrent pneumonias, stridor, recurrent coughs, irritability with feeding, apnea, and bradycardia (Mohan & Soni, 2002). GERD may be associated with significant sequelae including poor weight gain and chronic respiratory problems (Mohan & Soni, 2002). The reported incidence of GER in preterm infants varies and ranges from 22% up to 85% (Tipnis & Tipnis, 2009). The diagnosis of GER or GERD appears to be increasing in the infant population including healthy newborns and those infants hospitalized for a variety of reasons. Many of those hospitalized children are discharged home on some type of reflux medication (Orenstein & Hassall, 2007).

While evidence suggests that GER is common in most infants and that the incidence of GER decreases with increasing gestational age, there is a variety of treatment measures used in the neonatal intensive care unit (NICU) often without the diagnosis of GERD. These treatments are not without risks and side effects. While some treatments are as benign as elevating the head of an infant's bed to prevent reflux, others include medications that have been shown to increase the risk of other illnesses including acute gastroenteritis and pneumonia (Canani, et al, 2006).

### *Background to the Study*

Diagnosis of gastroesophageal reflux (GER) or gastroesophageal reflux disease (GERD) is sometimes difficult due to the controversy in diagnostic indicators. For example, the esophageal pH probe detects reflux of gastric contents by placing a pH probe into the lower third of the esophagus via nasal passage. The test measures the level of acidity of the reflux contents in the esophagus. This test can last up to 24 hours, and incorrect probe placement can produce inaccurate results. In addition, milk can act as a buffer to acidity after feedings which makes acid detection difficult (Martin & Hibbs, 2009). Intraluminal impedance, also known as multiple intraluminal impedance (MII), uses a catheter similar to a pH probe and measures the impedance from multiple intraluminal sensors. The detection of GER is based on changes in electrical resistance to current flow between electrodes. This is an emerging technology that may be better able to detect reflux (Martin & Hibbs, 2009).

Upper gastrointestinal studies with small bowel follow through can be used to detect GER, but these also have limitations. They require the use of barium which some infants have trouble tolerating. In addition, these studies capture a moment in time rather than a period over time. Unless the infant has an episode of reflux during this test, it will not be detected (Martin & Hibbs, 2009).

In the Neonatal Intensive Care Unit (NICU), gastroesophageal reflux is commonly reported by the nursing staff based on observable behaviors by infants including arching, irritability, desaturations, apnea, and bradycardia. Many infants are placed on a variety of pharmacologic agents to treat reflux, often without actual confirmed diagnosis of GERD. Pharmacologic therapies consist of acid suppression agents, such as H<sub>2</sub> receptor antagonists,

proton pump inhibitors, and prokinetic agents which improve gastric emptying. A common drug used to treat GERD is ranitidine, an H<sub>2</sub> receptor antagonist, but its efficacy in the treatment of GERD in infants has not been demonstrated (Martin & Hibbs, 2009).

Omeprazole and lansoprazole, both proton pump inhibitors, are used frequently in the treatment of GERD because of their acid reducing capabilities. There are concerns with using acid suppression agents because of the risks of both necrotizing enterocolitis and altered gastric colonizations (Martin & Hibbs, 2009).

Metoclopramide, a prokinetic agent, increases gastric emptying to decrease the amount of contents in the stomach. This drug is indeed used frequently in the pediatric population. However, the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition does not support its use in the pediatric population because there is limited clinical evidence of its efficacy (Vandenplas, et al, 2009).

### *Statement of the Problem*

Gastroesophageal reflux disease (GERD) treatment is not standardized. There are no clear guidelines to determine the use of pharmacologic or non-pharmacologic therapies depending on severity of disease. In addition, partially due to the controversies with diagnostic indicators, follow-up to determine effectiveness of the treatment used is inconsistent.

### *Purpose of the Study*

The purpose of this systematic review is to identify evidence-based practice guidelines for the treatment of GERD, including pharmacologic and non-pharmacologic interventions in the neonatal/infant population. In addition, treatment efficacy of

pharmacologic and non-pharmacologic modalities will be addressed.

### *Formal Research Question*

This research addresses the question: what are the best practices in the treatment of gastroesophageal reflux disease in the neonatal/infant population?

Answering the above question may help practitioners to better understand the treatment regimens associated with GERD. Evidence-based practice guidelines have the potential to decrease the usage of pharmacologic agents that may affect long term outcomes for infants, decrease side effects from their usage, and decrease costs to patients and families.

### *Significance of the Study*

The diagnosis and treatment of GERD varies greatly among practitioners and often the treatment comes without an actual diagnosis. In a recent study, Khoshoo, et al. (2009), showed that 42 of 44 infants were on antireflux medications with only 8 of these infants showing abnormal acid reflux on a pH probe study. The costs associated with the treatment of GERD, including the diagnosis and pharmacologic agents, continue to increase. A systematic review of available literature regarding neonates and infants with gastroesophageal reflux will help to identify best practices for the treatment of GERD in this population. This is important to healthcare administrators as some treatments may not be necessary or are used with an increased risk of additional illnesses. In addition, since the research shows that GERD may resolve over time (Suwandhi, et al, 2006), there is potential to use fewer pharmacologic agents. This has the potential to significantly decrease costs to families and decrease lost charges/reimbursements to hospitals. Attempts to standardize the treatment of GERD can improve the quality of care in the NICU and increase patient safety.

### *Definition of Terms*

Gastroesophageal reflux (GER) refers to the presence of gastric contents in the esophagus proximal to the stomach (Mohan & Soni, 2002).

Gastroesophageal reflux disease (GERD) is symptomatic GER and includes a variety of symptoms and observable events (Mohan & Soni, 2002).

Neonates are babies from birth to 4 weeks old.

Infants are babies from one month to 1 year old.

### *Organization of the Remainder of the Paper*

The following chapters will address the purpose, search strategy, levels of research, and grading of studies. Papers that met the inclusion criteria are summarized and are reported in the results section. The review provides suggestions for evidence-based guidelines for the treatment of GERD.

## Chapter 2. Methodology

### *Purpose/Question*

Gastroesophageal reflux disease (GERD) is treated frequently in the neonatal/infant population. This is often done without confirmatory diagnosis and without evaluation of efficacy. Some medications commonly prescribed for treatment are associated with side effects. In addition, these medications can be expensive, creating a burden for families. The question addressed by this project is: what are the best practices in the treatment of gastroesophageal reflux disease in the neonatal/infant population?

### *Research Methodology*

A systematic review of the literature was conducted for this study. Because there are not currently evidence-based practice guidelines for the treatment of gastroesophageal reflux disease, an analysis of the data is warranted. Systematic reviews are the cornerstone of evidence-based practice and, if performed in a structured way, are replicable. The Cochrane Consumer Network defines a systematic review as a study that summarizes available healthcare studies to provide a higher level evidence to increase the effectiveness of healthcare interventions (Cochrane Consumer Network, n.d.).

### *Search Strategy*

The following databases were searched for relevant articles: PubMed, CINAHL, MEDLINE, EMBASE, and the Cochrane Library. The following search terms were used in the search: gastroesophageal reflux, gastro-esophageal reflux, gastro-oesophageal reflux, drug therapy, diet therapy, and therapy. Only full text articles available through the Regis Library and The Children's Hospital Library were reviewed.

### *Inclusion Criteria*

1. Studies that address neonates and infants (babies from birth to 23 months) and preterm infants (those born before 37 weeks post conceptual age);
2. Studies that address treatments for gastroesophageal reflux;
3. Studies that include children up to 5 years old;

### *Exclusion Criteria*

1. Studies published prior to 2004;
2. Studies not published in English;
3. Studies that did not address gastroesophageal reflux as the main subject of the article;
4. Studies that address gastroesophageal reflux as a co-morbidity;
5. Studies that focus treatments on adults;
6. Studies that focus on surgical interventions as a form of treatment;
7. Studies that address subjects that have already had a surgical intervention for gastroesophageal reflux.

### *Grading of Studies*

Studies were assessed using the Level of Evidence Rating System for evaluation from Stetler, et al, (1998). The levels are summarized below:

#### **Levels of Evidence:**

- Level I: Meta-analysis or systematic review of multiple controlled studies or clinical trials
- Level II: Individual experimental studies with randomization
- Level III: Quasi-experimental studies such as nonrandomized controlled single-Group, pre-post, cohort, time series, or matched case-controlled studies

- Level IV: Nonexperimental studies, such as comparative and correlational descriptive research as well as qualitative studies
- Level V: Program evaluation, research utilization, quality improvement projects, case reports
- Level VI: Opinions of respected authorities; or the opinions of expert committee, including their interpretation of non-research based information.

Once each study is classified by level, grades will be assigned based on the following criteria:

- Grade A: Consistent level I studies
- Grade B: Consistent level II or III studies or extrapolations from level 1 studies
- Grade C: Level IV studies or extrapolations from level 2 or 3 studies
- Grade D: Level V or VI evidence or troublingly inconsistent or inconclusive studies of any level

Grade C and D studies will not be used in recommendations.

### *Sample Size*

Sample size was determined by the available data in the established published time frame. Saturation of the data was reached within the review articles. Eighty-six of the original 442 articles met the inclusion criteria and were used in the study.

### Chapter 3: Results

The initial search in PubMed which includes MEDLINE, EMBASE, and the Cochrane Database yielded 424 results. Of those 424 articles, 78 were duplicated. Two hundred and sixty one articles were removed due to the defined inclusion/exclusion criteria. The search of the CINAHL database yielded 18 articles. Twelve of those articles did not meet the inclusion criteria, four were duplicates. In total, 86 articles met the inclusion criteria and were assigned a research level according to the Stetler, et al, (1998) levels of evidence. This system assigns a level I rating to systematic reviews or meta-analysis and level II to individual experimental studies with randomization. This system assigns a level III rating to quasi-experimental studies such as nonrandomized controlled single-group, pre-post, cohort, time series, or matched case-controlled studies. A second reader was used to confirm levels of evidence. The results of this study are shown in Table I.

Much of the data in the systematic review articles were duplicated. Other articles recommended a tiered approach to care beginning with conservative therapies and progressing to more aggressive therapies if symptoms of gastroesophageal reflux continued. Systematic reviews dealt with one intervention or treatment that may or may not have been recommended.

The conservative therapies or approaches to the treatment of gastroesophageal reflux in neonates and infants found in the articles reviewed are summarized below:

- Parental reassurance is the easiest, least invasive treatment for infant regurgitation as symptoms usually decrease and disappear over time (Michail, 2007).
- Prone or left-lateral positioning after feedings can reduce GERD in preterm infants but cannot be used without cardiac monitoring because of the risk of SIDS (Corvaglia, et al, (2007).

- Faster gastric emptying can be seen with less liquid reflux and feeding on right side followed by change to left side after one hour (Van Wijk, et al, (2007).

If the above initial conservative therapies are not effective in the treatment of GERD, the next approach identified in the articles is to use therapies related to a change in the feeding process. Effective feeding strategies are listed below:

- Small, slow, and more frequent feedings (with frequent burping) in a relaxed environment are helpful to infants with delayed gastric emptying (Brodsky & Carr, 2006).
- Eliminating exposure to cow's milk (Vandenplas, et al, 2005).
- Thickened feedings can reduce regurgitation events but commercially available products may be better than additives because of the balanced nutrition in commercial products (Vandenplas, et al, 2005).
- Cornstarch can be used to thicken formula (Xinias, et al, 2005).
- Cereal thickened formula (rice or oatmeal) can be used to reduce the frequency of regurgitation (Chao & Vandenplas, 2007).
- Hypoallergenic formula is supported in infants with recurrent emesis (Suwandhi, et al, 2006).

If initial conservative therapies are unsuccessful in relieving symptoms of gastroesophageal reflux, some alterations in feedings have been shown to help. Brodsky & Carr (2006) identified that small, slow, and frequent feedings are helpful to infants with delayed gastric emptying. Vandenplas, et al, (2005) recommend the elimination of exposure to cow's milk as it may be efficacious for the reduction of symptoms of reflux.

There is a large amount of data both for and against the use of thickened feedings to

reduce the symptoms of GERD. In a study by Chao & Vandenplas (2007), cornstarch-thickened formula decreased the frequency of regurgitation and accelerated gastric emptying when compared to a more concentrated (125%) formula. Chao & Vandenplas, in another study, also showed that cereal-thickened formula is significantly more efficacious than positioning therapy in decreasing the frequency of regurgitation (Chao & Vandenplas, 2007). Xinias, et al, showed that a formula thickened with a specifically treated cornstarch reduced oesophageal reflux acid exposure and reduces the frequency of clinical symptoms (Xinias, et al, 2005). Smaller volume feeds thickened with rice cereal can alleviate symptoms of GERD but feeds thickened with oatmeal can have the same results with less difficulty in defecation (Mascarenhas, et al, 2005).

There are some studies looking at the effect of locust bean gum on gastroesophageal reflux. Miyazawa, et al (2007) showed a significant decrease in the number of regurgitation episodes with locust bean gum-thickened formula, although this study had a very small sample size and was non-randomized. In a randomized trial with two different concentrations of locust bean gum-thickened formulas, there was a decrease in the number of regurgitation episodes (Miyazawa, et al 2004). Although this may be important data, locust bean gum thickened formulas are not currently available in the United States. A study in 2007 showed that pre-thickened AR (anti-regurgitation) formulas showed that this formula is more effective in reducing the reflux index when GERD is more severe (Moukarzel, et al, 2007). Using a commercially available pre-thickened formula may be best because of nutritional concerns.

Pharmacotherapy can be useful in the treatment of gastroesophageal reflux disease although it should not be used as a first step in the treatment of reflux symptoms (Guimaraes, et al (2006). Effective medications are listed below:

- Gaviscon Infant can be used as it increases the viscosity of feeds and reduces reflux (Del Buono, et al, 2005).
- Ranitidine, an H<sub>2</sub> receptor antagonist, is successful in reducing gastric acidity, but long term gastric acid inhibitors can have sequelae (Tighe, et al, 2010).
- Omeprazole, a proton pump inhibitor, can only be limitedly recommended as it is not well studied in neonates and infants (Bishop, et al, 2007).
- Lansoprazole, a proton pump inhibitor, is well tolerated in neonates and infants but its efficacy is only established in children older than 1 year (Springer, et al, 2008).
- Esomeprazole, a proton pump inhibitor, does have acid suppressive effects in infants older than 1 month at a dose of 1mg/kg; systemic exposure in preterm infants and neonates at a dose of 0.5 mg/kg showed acid suppression but no effect on actual reflux events. This medication is only approved for use in children 1 year and older (Omari, et al, 2007).
- Cimetidine, a prokinetic agent, can be recommended limitedly for reduced regurgitation (Tighe, et al, 2010).

Gaviscon Infant, which acts as a feed thickener, prevents reflux by increasing the viscosity of feeds. In a study by Del Buono, et al, (2005), patients given Gaviscon did show a significant difference in reflux height in the esophagus when compared to placebo. It did not show a difference in the number of reflux events (Del Buono, et al, 2005).

Tighe, et al, (2010) report that ranitidine, cimetidine, and famotidine have shown efficacy superior to placebo for symptom relief and oesophageal healing in many clinical trials (Tighe, et al, 2010). Omeprazole has not been extensively studied in children. In a small study in children under 2 years, Bishop, et al, using pH studies to determine effectiveness, found the treatment

effective, with no serious complications or side effects. The sample size was very small. Lansoprazole is well studied for use. In a randomized, controlled trial in infants older than 3 months, the study group showed significant improvement in a shorter period of time when compared to the control group (Khoshoo and Dhume, 2008). Springer, et al, were able to show an increase in the percentage of time that intragastric pH was above 3, 4, 5, and 6 (less acidic) over the 24 hour post-dose period when compared to baseline. In contradiction with the previous studies, in a very large, well designed study, Orenstein, et al, detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants aged 1 to 12 months. It is difficult to rule out the use of lansoprazole because it appears to have very few side effects. Further studies are recommended to determine its efficacy.

Esomeprazole has been recently studied in children. In a study by Croxtall, et al, GERD symptoms improved significantly in children 1-11 years, but it was not studied in infants or children less than 1 year old (Croxtall, et al, 2008). In another randomized trial, Gilger, et al, showed that esomeprazole was well tolerated and symptoms of GERD were significantly reduced during the active treatment (Gilger, et al, 2008). Omari, et al, studied the effects of esomeprazole in infants 1 to 24 months old and found that it was well tolerated and showed acid suppression but not a decrease in the actual symptoms of GERD (Omari, et al, 2007). In a study focused on preterm and term neonates, Omari, et al, showed that esomeprazole caused significant acid suppression but had no effect on the frequency, type, and extent of impedance-detected bolus reflux. This study had no placebo control group so it is difficult to say that the improvements were caused by the drug or that they would have simply occurred over time (Omari, et al, 2009). Esomeprazole may be useful to treat GERD although there may not be visible signs of improvement in terms of reflux episodes.

In one study by Canani, et al, long term use of gastric acid inhibitors including H2 receptor antagonists and proton pump inhibitors was related to community acquired pneumonia and acute gastroenteritis. This is one reason that it is important to evaluate and re-evaluate the need for medications (Canani, et al, 2006).

There are several treatments and medications that can be ruled out for use, or require further study in order to be used, in the treatment of GERD in infants:

- Cisapride cannot be recommended for use because of serious side effects. This product has been removed from the market in the United States and is only available under compassionate care (MacLennan, et al, 2009).
- Domperidone cannot be recommended for use as its efficacy for the treatment of GERD cannot be determined in the target population (Cresi, et al, 2008).
- Metoclopramide has insufficient literature to support or oppose its use (Hibbs & Lorch, 2006).
- Nizatidine may have limited use. Further studies should be done to determine the efficacy of the drug (Orentstein, et al, 2005).
- Erythromycin efficacy has not been determined in neonates and infants (Tighe, et al, 2010).
- Baclofen has not been well studied in infants and needs further study (Omari, et al, 2006).
- Bethanechol has insufficient evidence to recommend use (Tighe, et al, 2010).
- Pantoprazole cannot be recommended as it is not studied in neonates and infants (Van Wijk, et al, 2007).
- Antacids and sucralfate, both aluminum containing, should not be used in infants (Vandenplas, et al, 2005).

The most difficult aspect of prescribing medications in neonates and infants is that with very little data in this age group, it is difficult to decide which medication to use to treat GERD. The medication chosen in the hospital setting appears to be driven more by physician preference than anything else.

Article Title/Author	Type of Article/ Study	Participants	Theme/Treatment	Outcomes	Level of Research/ Grade	Study strengths/ Weaknesses	Recommend for use in review
Pediatric Reflux: A Burp Gone Bad (2004, no author listed)	Patient handout; no references listed	Review article focusing on infants and older children	Focuses on feeding and formula types in infants; Focus on lifestyle changes, medications in older children	No outcomes listed	Level VI/Grade D	No recommendation for use	No
...Maybe They Can Be Avoided in Some Kids With Reflux (2008, no author listed)	Editorial within journal; short synopsis of study as a child health alert	Infants with suspected GERD	Conservative therapy; with no response, acid suppression therapy	No outcomes listed	Level VI/Grade D	No recommendation for use	No
Managing gastro-oesophageal reflux in infants (2009, no author listed)	Review article	Infants	Treatment should be initiated if growth is affected.	Dietary changes including eliminating exposure to cow's milk even with breastfeeding if symptoms severe; Short term nasogastric feeding for infants with poor weight gain; Thickening agents may be used to decrease incidents of regurgitation and increased weight gain; Positioning changes cannot be recommended; Gaviscon can be recommended with limitations; Cimetidine and Famotidine can be recommended limitedly for reduced regurgitation; Omeprazole can be used to reduce gastric acidity, acid exposure and number and duration of gastro-oesophageal reflux episodes.	Level I/Grade B	Review of Randomized Controlled Trials for Recommendations	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses/	Recommend for use in review
Developmental Pharmacokinetics and Pharmacodynamics of Nizatidine (2004, Abdel-Rahman, et al)	Non-randomized trial; open-label, single dose or multiple dose trial	Children aged 5 days to 18 years and adults aged 18-50 years	Nizatidine of various dosages.	The biodisposition of Nizatidine in children is similar to adults. Response after a comparable weight-based dose is equal and potentially greater in children.	Level III/Grade B	This study did not test the response but the disposition of the drug to determine dosage. Limited usage without trials to discuss efficacy.	Not without additional trials to discuss efficacy of Nizatidine for treatment of GERD
Infant Formulas Thickened with Carob Bean Gum Causing False-Positive Galactomannan Test Reactivity (2008, Aceti, et al)	Editorial Comment	Hospitalized children	Children on formulas thickened with carob bean gum can have false-positive Galactomannan test.	No outcomes listed	Level VI/Grade D	No recommendation for use	No
Protein Content and Fortification of Human Milk Influence Gastroesophageal Reflux in Preterm Infants (2009, Aceti, et al)	Case control study	17 preterm newborns fed naïve and fortified human milk	Human Milk fortification can increase the protein content in human milk and influence gastroesophageal reflux	An individualized fortification, based on the analysis of the composition of naïve human milk could optimize both nutrient intake and feeding intolerance	Level III/Grade B	Statistically significant in reflux episodes with increased protein content in fortified human milk ( $p < 0.05$ )	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Table I Outcomes	Level of Research /Grade	Study strengths/ Weaknesses/	Recommend for use in review
Anti-reflux or Anti-regurgitation Milk Products for Infants and Young Children: a Commentary by the ESPGHAN Committee on Nutrition (2004, Agostini, C. on behalf of ESPGHAN Committee of Nutrition)	Editorial comment	Infants and young children	Formula with thickening agents to decrease regurgitation and reflux	No outcomes noted	Level VI/Grade D	Formulas with thickening agents should not be used indiscriminately.	No
The Reflex to Treat Reflux – Let’s be Conservative Regarding Gastroesophageal Reflux (GER)! (2008, Balistreri, W.F.)	Editorial comment	Infants and Children	Conservative therapy for GERD should be used in infants. Medications may be overprescribed in this population	No outcomes noted	Level VI/Grade D	No recommendation for use	No
Lack of Age-Appropriate RCTs Make Evidence-Based Treatment Difficult (2005, Bell, A. L.)	Editorial comment	Infants	Treatment with medications if conservative therapy fails is not well supported with clinical trials	No outcomes noted	Level VI/Grade D	No recommendation for use	No

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Gastro-oesophageal Reflux Disease in Preterm Infants: Current Management and Diagnostic Dilemmas (2009, Birch & Newell)	Review Article	Preterm Infants	Conservative therapy for treatment should be utilized before moving to more advanced treatments	Prone or left-lateral positioning reduces GORD in preterm infants, should only be used in hospitalized infants with cardio respiratory monitoring. Evidence is limited for the beneficial effects of thickeners. Carob-based thickeners reduce non-acid reflux in older infants. No good evidence for the use of Erithromycin. Ranitidine is successful in reducing gastric acidity. Cimetidine not recommended in preterm infants. There is no evidence that Proton pump inhibitors are more effective than ranitidine in treating GORD and their safety is not well studied. Domperidone not recommended in preterm infants.	Level I/Grade B	Review of trials for preterm infants; Suggested management strategy from conservative therapy to more advanced treatments.	Yes
Omeprazole for Gastroesophageal Reflux Disease in the First 2 Years of Life: A Dose Finding Study with Dual Channel pH Monitoring (2007, Bishop, et al)	Prospective Dose-finding study	Children under 2 years of age	Treatment with Omeprazole	Omeprazole is an effective treatment for gastroesophageal reflux disease in children younger than 2 ( $p < 0.05$ ) although sample size was small (10 children).	Level III/Grade B	Used pH studies to determine effectiveness, no serious complications or side effects.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Extraesophageal Reflux in Children (2006, Brodsky and Carr)	Review article	Children (infants to adolescents)	Conservative treatments including environmental exposures and feeding alterations should be considered before medications	<p>Infants: Soy, partially hydrolyzed, and elemental formulas can be helpful. Small, slow, and frequent feedings in a relaxed environment are helpful to infants with delayed gastric emptying. Thickening of formula should be avoided.</p> <p>Children aged 2-11 years: Spicy, acidic, caffeinated and fatty foods should be avoided. Carbonated beverages should be avoided.</p> <p>Little support for medications in children noted.</p>	Level I/Grade B	Review article. Studies not cited within article.	Yes/Limited
Therapy with Gastric Acidity Inhibitors Increases the Risk of Acute Gastroenteritis and Community-Acquired Pneumonia in Children (2006, Canani, et al)	Non-randomized control trial	Children aged 4-36 months	Treatment of gastroesophageal reflux with gastric acid inhibitors.	The use of gastric acid inhibitors is associated with an increased risk of acute gastroenteritis and community-acquired pneumonia in children with GERD.	Level III/Grade B	Large sample size. Low p-values for statistical significance. Use caution when prescribing gastric acid inhibitors.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Comparison of the Effect of a Cornstarch thickened Formula and Strengthened Regular Formula on Regurgitation, Gastric Emptying and Weight Gain in Infantile Regurgitation (2007, Chao & Vandenplas)	Prospective Randomized Trial – infant used as own control – for two different interventions	Infants with regurgitation/ vomiting $\geq 3$ times per day	Cornstarch thickened formula vs. 25% strengthened regular infant formula (five scoops instead of 4 scoops to 120mL of water).	Cornstarch-thickened formula feeding decreases the frequency of regurgitation/vomiting, provides better body weight gain and has an accelerated gastric emptying in comparison to a 25% strengthened regular formula in infants with regurgitation.	Level II/Grade B	Fairly large sample size, focused on infants, with low p values for statistical significance. Randomized trial using infant as own control.	Yes
Effect of Cereal-Thickened Formula and Upright Positioning on Regurgitation, Gastric Emptying, and Weight Gain in Infants with Regurgitation (2007, Chao & Vandenplas)	Prospective randomized trial	Infants 2 to 6 months of age with regurgitation or vomiting at least 3 times per day	Cereal-thickened formula versus postprandial upright position for 90 minutes.	Cereal-thickened formula is significantly more efficacious than postural therapy in decreasing the frequency of regurgitation. Cereal thickened formula also results in an increased caloric intake (approximately 25%) related to increased gain in weight and length in comparison with regular formula and positioning therapy.	Level II/Grade B	Fairly large sample size. Focused on infants. Statistically significant results.	Yes
Patience is a Virtue in the Management of Gastroesophageal Reflux (2009, Clark & Spitzer)	Editorial comment	Children	Conservative therapies often decrease symptoms of reflux – more advanced therapies may not be necessary.	No outcomes noted	Level VI/Grade D	No recommendation for use	No

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Starch Thickening of Human Milk is Ineffective in Reducing the Gastroesophageal Reflux in Preterm Infants: A crossover Study Using Intraluminal Impedance (2006, Corvaglia, et al)	Crossover Trial	Preterm infants	Thickening of fortified human milk by precooked starch.	Thickening human milk by precooked starch is ineffective in reducing gastroesophageal reflux in premature infants	Level III/Grade B	Small sample size. Because of risk of necrotizing enterocolitis with thickened milk in pre-term infants, would not recommend starch thickening	Yes
The Effect of Body Positioning on Gastroesophageal Reflux in Premature Infants: Evaluation by Combined Impedance and pH Monitoring (2007, Corvaglia, et al)	Non-randomized, using subject as their own control	Preterm infants	Positioning in the prone or left lateral position and its effect on gastroesophageal reflux	Placing premature infants in the prone or left lateral position in the postprandial period is a simple intervention to limit GER.	Level III/Grade B	Small sample size but statistically significant results. Non-invasive intervention.	Yes
Short-term Effect of Domperidone on Gastroesophageal Reflux in Newborns Assessed by Combined Intraluminal Impedance and pH Monitoring (2008, Cresi, et al)	Randomized controlled trial	Term and Preterm neonates	Use of Domperidone to decrease the number of reflux episodes	There was a paradoxical increase in the number of GER episodes in the treatment group. This treatment may not be efficacious in this age bracket.	Level II/Grade B	Small sample size with statistically significant results. Would not use this treatment in this age group as more studies are needed.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Gaviscon for Gastro-oesophageal Reflux in Infants: a Poorly Effective Treatment? (2006, Cresi, et al)	Editorial comment	Infants	Gaviscon for reflux treatment	No outcomes noted	Level VI/Grade D	No recommendation for use	No
Lansoprazole In the Treatment of Gastro-Oesophageal Reflux Disease in Children and Adolescents (2005, Croom & Scott)	Open-label, uncontrolled trial	Children aged 1-11 years. Adolescents aged 12-17 years.	Drug treatment (proton pump inhibitor) that inhibits gastric acid secretion	The effectiveness and tolerability of Lansoprazole has been established in pediatric patients aged 1-17 years for short-term treatment of symptomatic GORD and erosive oesophagitis.	Level III/Grade B	Does not look at infants and children less than 1 year of age. Not a randomized-controlled trial.	Yes/Limited to children 1 year old or older
Esomeprazole in Gastroesophageal Reflux Disease in Children and Adolescents (2008, Croxtall, et al)	Randomized, double-blind, multicenter trial	Children aged 1-11 years. Adolescents aged 12-17 years.	Drug treatment (proton pump inhibitor) that inhibits gastric acid secretion	GERD symptoms significantly improved with Esomeprazole in children aged 1-11 years and adolescents aged 12-17 years in. Esomeprazole was generally well tolerated in both children and adolescents.	Level II/Grade B	Does not look at infants and children less than 1 year of age.	Yes/Limited to children 1 year old or greater.
Effect of Gaviscon Infant on Gastro-oesophageal Reflux in Infants Assessed by Combined Intraluminal Impedance/pH (2005, Del Buono, et al)	Randomized, placebo controlled, double blind study	Children under 12 months of age.	The influence of Gaviscon Infant on Gastro-oesophageal Reflux in infants	Results showed a marginal but significant difference between Gaviscon Infant and placebo in average reflux height. The treatment did not show a significant difference in median number of reflux events per hour, acid reflux events per hour, minimum distal or proximal pH, total acid clearance time per hour and total reflux duration per hour between treatment and placebo.	Level II/Grade B	Good study design, small number of subjects. Does not appear to be a perceived clinical benefit to the treatment's use.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Does Treating Gastroesophageal Reflux Cause Pneumonia? (2005, Federico, M)	Editorial Comment	Infants and children	Relationship between proton pump inhibitor or H2 blocker use for the treatment of GER and community-acquired pneumonia	No outcomes noted	Level VI/Grade D	No recommendation for use	No
Systematic Review: Proton Pump Inhibitors for the Treatment of Gastroesophageal Reflux in Infants (2008, Gieruszczak-Bialek, et al)	Systematic Review	Infants	Review to evaluate the efficacy and safety of proton pump inhibitors for the treatment of GERD in infants.	There is insufficient evidence to determine the role of proton pump inhibitor therapy for treatment of GERD in infants. Further trials are needed addressing both safety and efficacy of proton pump inhibitors in infants.	Level I/Grade A	Review of randomized controlled trials.	Yes
Safety and Tolerability of Esomeprazole in Children with Gastroesophageal Reflux Disease (2008, Gilger, et al)	Multicenter, randomized, uncontrolled, double-blind study.	Children aged 1 to 11 years.	Treatment with Esomeprazole for gastroesophageal reflux disease	In children with endoscopically proved GERD, Esomeprazole was generally well tolerated. Frequency and severity of GERD-related symptoms significantly reduced during active treatment period.	Level II/Grade B	Well designed study. Large sample size. Low P values for statistical significance.	Yes/Limited
Gastroesophageal Reflux Disease: Could Intervention in Childhood Reduce the Risk of Later Complications? (2004, Gold, B. D.)	Review article	Children	Do treatments for gastroesophageal reflux disease in children reduce the risk of later complications in adulthood?	Treatments for pediatric GERD are based on the clinical indications of the specific child with GERD and range from conservative measures (positioning, formula changes) to pharmacotherapy to surgery. Proton pump inhibitors are safe, effective, and due to their superiority in resolving acid related disease, could be appropriate interventions in GERD occurring in childhood to successfully prevent long term sequelae.	Level I/Grade B	Review article with current data. No specific reference to infants.	Yes/Limited

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Treatment of Gastroesophageal Reflux Disease (2006, Guimaraes, et al)	Review article	Infants and Children	Treatment of gastroesophageal reflux disease with emphasis on pharmacological aspects.	Left lateral and prone positioning should only be considered in infants if the risks related to GERD outweigh the risk of sudden infant death syndrome. There is no benefit to inclined positions. Thickened formulas may reduce clinical symptoms but not actual reflux in the esophagus. Avoiding spicy, caffeinated foods and chocolate is recommended in older children. H2 receptor antagonists and proton pump inhibitors have some support for use.	Level I/Grade A	Review article of controlled and randomized trials and review articles.	Yes
Gastroesophageal Reflux and Prokinetic Agents (2005, Hammer, D.)	Review article	Preterm and term infants	Treatment of GER with prokinetic agents.	Non-pharmacologic agents are the first step in treating GER including positioning and feeding interventions. Bethanechol is not recommended for treatment. Erythromycin is not recommended for treatment. Metoclopramide can be recommended for use.	Level I/Grade B	Review article looking at preterm and term infants.	Yes
Talk is Cheap, Often Effective: Symptoms in Infants Often Respond to Non-pharmacologic Measures (2008, Hassall, E.)	Editorial comment	Infants	Non-pharmacologic treatment of gastroesophageal reflux	No outcomes noted	Level VI/Grade D	No recommendation for use	No

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Characteristics of Children Receiving Proton Pump Inhibitors Continuously for Up to 11 Years Duration (2007, Hassall, et al)	Retrospective cohort study	Children aged less than 1 year to 17 years old.	Long-term treatment with proton pump inhibitors for gastroesophageal reflux disease.	Children with long term proton pump inhibitor use have few adverse reactions and discontinuation of the drug is seldom indicated. Preliminary data suggest that proton pump inhibitors may be efficacious and safe for continuous use for up to 11 years duration in children.	Level III/Grade B	Cohort study with large sample size.	
Domperidone Versus Cisapride in the Treatment of Infant Regurgitation and Increased Acid Gastro-oesophageal Reflux: A Pilot Study (2009, Hegar, et al)	Investigator-blinded, prospective comparative trial.	Infants regurgitating more than 4 times per day for more than 2 weeks after conservative treatment failure.	Prokinetic therapy for the treatment of gastroesophageal reflux symptoms.	The frequency of regurgitation decreased in both groups although more rapidly in the Cisapride group. The decrease in regurgitation was still significant after 1 month. The natural decrease in the incidence of regurgitation induced by age should also be considered.	Level II/Grade B	Pilot study with small sample size. Blinded, prospective, comparative trial with no controls.	Yes/Limited
Natural Evolution of Infantile Regurgitation Versus the Efficacy of Thickened Formula (2008, Hegar, et al)	Prospective, blinded, randomized 1-month intervention trial	Healthy, term-born, formula-fed infants aged 1 to 3 months.	Therapy of parental reassurance in combination with standard infant formula, 5 grams of rice cereal added to 100mL standard formula, or formula manufactured with bean gum as a thickening agent.	Thickening of formula decreases regurgitation, but not significantly. Parental reassurance remains the cornerstone of the treatment of infant regurgitation.	Level II/Grade B	Sample size of 60 infants. Randomized trial with statistically significant results.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Table I Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Pharmacokinetics and Pharmacodynamics of Lansoprazole in Children 13 to 24 Months Old With Gastroesophageal Reflux Disease (2007, Heyman, et al)	Subanalysis of 8 toddlers who participated in a phase I/II open-label, multicenter US study	8 toddlers between 13 and 24 months.	Treatment with Lansoprazole increased if symptomatic after 2 weeks of treatment	Lansoprazole displays pharmacokinetic and pharmacodynamic parameters in children between 13 and 24 months of age that are similar to those results observed in older children as well as adults. Further studies are needed to confirm results.	Level III/Grade B	Very small sample size. Non-randomized trial.	Yes/Limited
Metoclopramide for the Treatment of Gastroesophageal Reflux Disease in Infants: A Systematic Review (2006, Hibbs & Lorch)	Systematic Review	Infants	Treatment with Metoclopramide for gastroesophageal reflux disease.	11 prospective trials, 5 were randomized, blinded clinical trials. The current literature is insufficient to either support or oppose the use of Metoclopramide for gastroesophageal reflux disease in infants.	Level I/Grade A	Inconclusive recommendation for usage. Further trials needed.	Yes
The Effect of Thickened-Feed Interventions on Gastroesophageal Reflux in Infants: Systematic Review and Meta-analysis of Randomized, Controlled Trials (2008, Horvath, et al)	Systematic Review with meta-analysis	Infants	Effect of feed thickeners on gastroesophageal reflux disease.	Thickened food is only moderately effective in treating gastroesophageal reflux in term infants. The data did not allow the authors to conclude whether any particular thickening agent is definitely more effective than another.	Level I/Grade A	Used Randomized Controlled Trials.	Yes/Limited

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Table I Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Feed Thickener for Newborn Infants With Gastro-oesophageal Reflux (2009, Huang, et al)	Systematic Review	Newborn Infants	The use of feed thickeners in reducing signs and symptoms of GOR, acid episodes on pH monitoring and histological evidence of oesophagitis.	No suitable studies were found for inclusion in the review.	Level I/Grade A	Reviewed randomized, controlled trials.	Yes/Limited
Gastroesophageal Reflux in Preterm Infants: How Acid Should It Be? (2008, Indrio, et al)	Editorial comment	Preterm Infants	Effect of proton pump inhibitors on gastroesophageal reflux.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No
Update on Drugs for Gastro-oesophageal Reflux Disease (2007, Keady, S.)	Review article	Infants, children and adolescents	Review of management techniques to treat gastro-oesophageal reflux disease.	Antacids can be used as first line medication although there are not long-term effects. Gaviscon Infant can be used. Domperidone shows very little efficacy. Erythromycin efficacy in neonates and infants has not been supported by clinical trials. Metoclopramide has limited use as adverse effects are severe. The product license for Cisapride has been withdrawn. Ranitidine has efficacy in mild oesophagitis. Proton pump inhibitors such as Lansoprazole and Omeprazole show benefit but children seem to metabolize them quicker so a daily dose regimen may be necessary. Lack of child suitable formulations can limit their use.	Level I/Grade B	Review did not include only randomized controlled trials.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Clinical Response to 2 Dosing Regimens of Lansoprazole in Infants With Gastroesophageal Reflux (2008, Khoshoo and Dhume)	Randomized Controlled Trial	Infants older than 3 months born at term.	To determine the clinical efficacy of 2 dosing regimens of Lansoprazole in infants with GERD.	The two different doses had better results for infants than those in the control group. The group with the twice daily doses showed significant improvement in a shorter period of time. There may be a faster onset of symptom improvement but eventually there was no difference between the two doses overall.	Level II/Grade B	Randomized controlled trial. 66 participants in the study, reasonable sample size.	Yes
Soothing Your Breastfed Baby With Reflux (2009, Kombol, P.)	Parent Handout	Breastfed infants up to 1 year of age	Feeding interventions to deal with gastroesophageal reflux.	No outcomes noted	Level VI/Grade D	No recommendation for use.	No
Treating GER in Children Younger Than Two Years (2005, Kripke, C.)	Editorial comment	Children younger than 2 years.	Conservative therapy for the treatment of GER.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No
FDA Approves Nexium for Use in Children Ages 1-11 Years (2008, Lang, L.)	Bulletin	Children aged 1-11 years.	Treatment approved for use in gastroesophageal reflux disease.	No outcome noted.	Level VI/Grade D	No recommendation for use.	No

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Table I Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Use of Medications for Gastroesophageal Reflux at Discharge Among Extremely Low Birth Weight Infants (2008, Malcolm, et al)	Retrospective cohort analysis	Extremely low birth weight infants at corrected ages of 18 to 22 months.	Medication usage in the treatment of gastroesophageal reflux disease and the effect on growth or development at the time of follow-up evaluations.	Use of antireflux medications at the time of discharge for extremely low birth weight infants does not seem to have effects on growth or development. Medications included were antacids and H2 receptor antagonists.	Level III/Grade B	Large sample size. Medication types not broken down into groups.	Yes
Drugs for the Treatment of Gastro-oesophageal Reflux: In Search of Clear Evidence-based Indications (2007, Marchetti, et al)	Editorial comment	Infants	Drugs for the treatment of gastroesophageal reflux disease.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No
Gastroesophageal Reflux in Preterm Infants: Is Positioning the Answer? (2007, Martin, et al)	Editorial comment	Preterm Infants	Positioning as the treatment for gastroesophageal reflux.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No
Difficulty in Defecation in Infants with Gastroesophageal Reflux Treated with Smaller Volume Feeds Thickened with Rice Cereal (2005, Mascarenhas, et al)	Non-randomized, case control study.	Full-term, neurologically intact infants less than 5 months of age.	Treatment of rice cereal thickened, small volume feeds for gastroesophageal reflux and its relation to difficulty with defecation.	Smaller volume feeds thickened with rice cereal was effective in alleviating symptoms of GER but about one third of the infants had difficulty with defecation. Changing rice to oatmeal resulted in partial or complete improvement in defecation difficulty in about 70% of these infants without causing a change in symptoms of gastroesophageal reflux.	Level I/Grade B	Study design limited. The measurement of symptoms of gastroesophageal reflux was likely inadequate.	Yes/Limited

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Cisapride Treatment for Gastro-Oesophageal Reflux in Children (2009, MacLennan, et al)	Systematic Review	Children diagnosed with gastro-oesophageal reflux	Does Cisapride reduce symptoms of gastro-oesophageal reflux?	Ten trials in total met the inclusion criteria for this systematic review. There was no clear evidence that Cisapride reduces symptoms of gastro-oesophageal reflux.	Level I/Grade A	Review used randomized controlled trials for review. Cisapride not recommended for use and treatment is limited to patients treated within a clinical trial program.	Yes
Gastroesophageal Reflux (2007, Michail, S.)	Review article	Pediatric population	Appropriate therapies for gastroesophageal reflux disease.	Reassurance and educating the family in an otherwise healthy infant can be the only intervention in some. Lifestyle changes can be helpful for children with mild disease. Feeding interventions would be the next intervention for moderate disease. Prone positioning can be used only when there is no risk of death from SIDS. Antacids can be used for short-term therapy and relieve of symptoms. H2 receptor antagonists have demonstrated efficacy esophagitis but not as well as proton pump inhibitors. Surface agents should be used with caution.	Level I/Grade B	Review article. Not limited to randomized controlled trial review.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Table I Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Effect of Formula Thickened with Reduced Concentration of Locust Bean Gum on Gastroesophageal Reflux (2007, Miyazawa, et al)	Non randomized case-control study.	Infants less than 2 months old who had three or more episodes of regurgitation or vomiting per day.	Treatment with locust bean gum thickened formula for gastroesophageal reflux disease.	The median number of regurgitation episodes decreased significantly ( $p=0.00048$ ) with the thickened formula. No significant difference was evident in feeding volume and time, body weight gain, or gastric emptying rate between thickened and non-thickened formula.	Level III/Grade B	Small study number (20), but used infants as their own control.	Yes
Effect of Locust Bean Gum in Anti-regurgitant Milk on the Regurgitation in uncomplicated Gastroesophageal Reflux (2004, Miyazawa, et al)	Randomized, controlled crossover trial	Infants with daily regurgitation but no other medical problems	Effect of different concentrations of locust bean gum in anti-regurgitant milk on gastroesophageal reflux.	Both concentrations of AR formulas decreased the number of regurgitation episodes by about 50%. The decreased concentration of locust bean gum may be easier for the infant to suck through the nipple.	Level II/Grade B	Small sample size (30) but a randomized controlled crossover trial.	Yes
Effect of Formula Thickened with Locust Bean Gum on Gastric Emptying in Infants (2006, Miyazawa, et al)	Randomized controlled trial	Infants with three or more episodes of regurgitation per day without other major medical problems.	Two different formulas with two different concentrations of locust bean gum compared to a control formula without locust bean gum and their effect on gastric emptying.	Thickened formula with locust bean gum slowed gastric emptying more than one with a reduced concentration of this thickening agent and more than a formula without a thickening agent. However, thickened formulas reduced the number of regurgitation episodes after feeding, without causing any complications.	Level II/Grade B	Randomized, controlled trial with fair sample size. Formulas thickened with locust bean gum are not readily available in the United States.	Yes/Limited

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Effects of a Prethickened Formula on Esophageal pH and Gastric Emptying of Infants with GER (2007, Moukarzel, et al)	Randomized controlled trial	74 healthy infants less than 6 months old with GER.	Prethickened formula used for infants with GER and their effect on gastric pH and gastric emptying. A reflux index score was used to measure severity of reflux disease.	This studies was able to show a significant ( $p < 0.01$ ) improvement in the reflux index of infants who received the AR (anti-regurgitation, pre-thickened) formula. There was also significantly faster clearance from the esophagus of AR than regular formula which was a difference of almost one minute. The longest reflux episode of the AR fed group was significantly shorter than the longest reflux episode of the regular formula fed group. The study suggests that AR formula is more effective in reducing the reflux index when GER is more severe.	Level II/Grade B	Randomized controlled trial with moderate sample size. Excellent P values for statistical significance.	Yes
Gastroesophageal Reflux in Infants: Can a Simple Left Side Positioning Strategy Help This Diagnostic and Therapeutic Conundrum? (2008, Omari, T.)	Review Article	Preterm and term infants from 0-6 months of age.	Left-sided positioning as a non-pharmacological approach to the treatment of GER related symptoms.	Left side positioning will reduce the number of reflux events in infants and is likely to complement standard proton pump inhibitor therapy. It has not been proven that left side positioning will reduce symptoms due to gastroesophageal reflux in infants. Left side positioning can increase the risk of SIDS and should only be used for short periods of time (2 hours post prandial) and not overnight when an infant is unobserved.	Level I/Grade B	Review article focusing on position in the treatment. Not a systematic review.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Pharmacokinetics and Acid-suppressive Effects of Esomeprazole in Infants 1-24 Months Old with Symptoms of Gastroesophageal Reflux Disease (2007, Omari, et al).	Single-blind, randomized, parallel-group study	50 infants 1 to 24 months old with symptoms of GERD	Treatment with esomeprazole and its effect on GERD	Oral treatment with esomeprazole 0.25 mg/kg and 1 mg/kg was well tolerated and provided dose-related acid suppression, dose-related exposure to esomeprazole and decreased esophageal acid exposure in infants. The dosage of 1 mg/kg provided the most effective acid suppression, normalizing esophageal acid exposure in this group of patients. The effect of esomeprazole on symptoms of GERD in the infants participating in the trial were inconclusive because there were no obvious changes in vomiting, choking/gagging and irritability/crying symptom scores during 1 week of treatment.	Level II/Grade B	Randomized study with good sample size. No placebo control within study.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Pharmacodynamics and Systemic Exposure of Esomeprazole in Preterm Infants and Term Neonates with Gastroesophageal Reflux Disease (2009, Omari, et al).	Open-label trial	Preterm infants and term neonates aged < 1 month term age.	Treatment with esomeprazole for GERD	Esomeprazole 0.5 mg/kg given once daily showed significant acid suppression but had no effect on the frequency, type, and extent of impedance-detected bolus reflux. Despite increased systemic exposure, treatment with esomeprazole was well tolerated, and significant acid suppression was apparent, indicating that the chosen dosage of 0.5 mg/kg once daily is appropriate in the preterm infant and term neonate population. The number of symptoms overall, as well as individual symptoms of gagging and irritability/crying, were significantly reduced on therapy.	Level III/Grade B	No placebo control group. Difficult to say that treatment caused improvements versus improvement that might have occurred over time. Good sample size.	Yes
Effect of Baclofen on Esophagogastric Motility and Gastroesophageal Reflux in Children with Gastroesophageal Reflux Disease: A Randomized Controlled Trial (2006, Omari, et al).	Randomized Controlled Trial	Children aged 2.6 years to 17.4 years.	Trial to look at the effects of Baclofen on motility and gastroesophageal reflux.	Baclofen significantly reduced the rate of triggering of transient lower esophageal sphincter relaxation (TLESR) and GER but did not reduce the rate of swallowing, the pattern of peristalsis or the magnitude of lower esophageal sphincter pressure compared with placebo. Baclofen reduced the triggering of TLESRs in children and this was associated with a reduced number of GER episodes. Baclofen also increases gastric emptying.	Level II/Grade B	Randomized controlled trial. 30 children enrolled. Does not specifically study the effects on infants. This study did not address how well long term therapy with Baclofen would be tolerated in children.	Yes/Limited

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Nizatidine for the Treatment of Pediatric Gastroesophageal Reflux Symptoms: An Open-Label, Multiple-Dose, Randomized, Multicenter Clinical Trial in 210 Children (2005, Orenstein, et al).	Randomized, parallel group, open-label, multiple-dose, multicenter study.	Children aged 5 days through 12 years and 13 years through 18 years.	Treatment with Nizatidine in various doses and formulations for gastroesophageal reflux disease.	Tolerability of nizatidine is supported in the current study. 8 weeks of treatment with nizatidine were accompanied by complete resolution of all reflux symptoms in nearly one third of the children in the treatment groups. There was an overall improvement in symptoms and a decrease in antacid use in the pediatric study population. Formulation did not appear to alter tolerability or effectiveness.	Level II/Grade B	Open label design. Large sample size. Multiple dosing and formulation groups modulate the power of the study.	Yes/Limited
Infants and Proton Pump Inhibitors: Tribulations, No Trials (2007, Orenstein & Hassall).	Editorial Comment/ Expert opinion	Infants	Treatment with proton pump inhibitors for the treatment of gastroesophageal reflux.	No outcome noted.	Level VI/Grade D	No recommendation for use.	No
Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial Assessing the Efficacy and Safety of Proton Pump Inhibitor Lansoprazole in Infants with Symptoms of Gastroesophageal Reflux Disease (2009, Orenstein, et al).	Double-blind, randomized, placebo-controlled trial	Infants aged 28 days to < 12 months and preterm infants with corrected age of 44 weeks PCA but < 12 months.	Treatment with lansoprazole for gastroesophageal reflux disease.	This study detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants aged 1 to 12 months. Significant adverse events, particularly lower respiratory tract infections occurred more frequently with lansoprazole than with placebo.	Level II/Grade B	Good study design. Power was suggested at 160 subjects, 162 enrolled. Crying was a part of the inclusion criteria and is nonspecific for GERD.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Efficacy of Conservative Therapy as Taught in the Primary Care Setting for Symptoms Suggesting Infant Gastroesophageal Reflux (2008, Orenstein & McGowan).	40 of the 50 infants enrolled in the Prospective, double-blind, placebo-controlled randomized clinical trial of an oral solution of an H2RA.	Infants	Conservative therapy taught in the primary care setting and its impact on symptoms of gastroesophageal reflux disease.	Two weeks of conservative therapy measures can improve symptoms in 78% of infants with GERD who are seen and treated in the primary care setting, normalizing symptoms in 24%.	Level II/Grade B	Non randomized trial. Small sample size. Conservative therapy can be initiated without side effects to patients.	Yes
Should Domperidone Be Used For the Treatment of Gastro-oesophageal Reflux in Children? Systematic Review of Randomized Controlled Trials in Children Aged 1 Month to 11 Years Old (2005, Pritchard, et al).	Systematic review of randomized controlled trials.	Children aged 1 month to 11 years old.	Domperidone for the treatment of gastroesophageal reflux disease	There was limited evidence available. There was no robust evidence of efficacy for the treatment of GOR with domperidone in young children.	Level I/Grade A	Review of randomized controlled trials.	Yes
Letter To The Editor (2005, Puntis, J. W. L.)	Editorial comment/ expert opinion	Babies	The use of carob bean gum thickeners for treatment of gastroesophageal reflux.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Stop the PPI Express: They Don't Keep Babies Quiet! (2009, Putnam, P. E.)	Editorial comment/ expert opinion	Babies	Treatment with proton pump inhibitors and their affect on gastroesophageal reflux.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No.
Commentary (2005, Ravazzolo, C. J.)	Editorial comment/ Expert opinion	Infants	Treatments for gastroesophageal reflux.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No.
Commentary (2008, Savino & Castagno)	Editorial comment/ Expert opinion	Infants	The use of thickened formulas for the treatment of gastroesophageal reflux.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No.
Overprescription of Antireflux Medications for Infants With Regurgitation (2008, Savino & Castagno)	Editorial comment/ Expert opinion	Infants	Use of antireflux medications for infants with regurgitation.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No.
Pediatric Gastroesophageal Reflux Disease Case Study (2009, Smith, et al)	Case study	Infant	Case study showing manifestations of GERD in an infant beginning at 7 months of age.	Outcome of the combination of pharmacotherapy with Lansoprazole, nutritional supplementation, and behavioral therapy were successful in treating GERD.	Level VI/Grade D	No recommendation for use.	No

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Non-pharmacologic Therapy May Be Effective For Infants With Gastroesophageal Reflux (2008, Sondheimer, J.)	Editorial Comment/expert opinion	Infants	Conservative therapy in the treatment of GERD.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No
Safety and Pharmacodynamics of Lansoprazole in Patients with Gastroesophageal Reflux Disease Aged < 1 Year (2008, Springer, et al).	Single and repeated dose, randomized, parallel-group, open-label, multicenter study	Infants less than 1 year of age.	Effect of lansoprazole on the symptoms of GERD.	Over 5 days of daily dose administration, lansoprazole was well tolerated in neonates and infants. Lansoprazole increased the percentage of time that intragastric pH was above 3, 4, 5, and 6 over the 24 hour post-dose period on days 1 and 5 when compared to baseline. A decrease in the frequency of GERD symptoms was also observed although the study was not designed to assess clinical benefit in children <1 year of age.	Level II/Grade B	Good study design. Small sample size at 24 infants.	Yes
Gastroesophageal Reflux in Infancy and Childhood (2006, Suwandhi, et al).	Review Article	Infants and Children	Review looking at GERD and its symptoms, diagnosis and treatments.	Treatment objectives are relief of symptoms. Avoidance of certain foods that exacerbate acid reflux, lifestyle modifications, nutritional changes including thickening of feeds. Hypoallergenic formula is supported in infants with recurrent emesis. H2 receptor antagonists or proton pump inhibitors would be the next line of treatment. Prokinetic drugs remain controversial for treatment. Next step surgical intervention.	Level I/Grade B	Review article focusing on infants and children.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Effect of an Amino Acid-based Milk – Neocate – on Gastro-oesophageal Reflux in Infants Assessed by Combined Intraluminal Impedance/pH (2006, Thomson, et al).	Non randomized study with patients as their own control.	Infants under 12 months of age with clinically suggestive symptoms of GOR.	Treatment with Neocate to impact symptoms of GOR.	The trial revealed a symptomatic improvement on Neocate but cannot be attributed to any positive effect on GOR. There was no observable difference in any reflux parameter as measured by two methods.	Level III/Grade B	Non-randomized. Very small sample size of 11 infants.	Yes
Histamine H2 Receptor Antagonists and Proton Pump Inhibitors: Best Options for Gastro-oesophageal Reflux in Children (2010, Tighe, M., et al).	Review article.	Children	Best pharmacotherapy for the treatment of GOR.	Conservative approaches can assist in the treatment of GOR. H2 receptor antagonists decrease acid secretion. Ranitidine, cimetidine and famotidine have shown efficacy superior to placebo for symptom relief and oesophageal healing in many clinical trials. Proton pump inhibitors are considered the most effective acid suppressant medications. There is no data for use in infants under the age of 6 months or on the long-term safety in children. Prokinetic agents such as Metoclopramide and Domperidone, limited benefit. There is insufficient evidence to recommend erythromycin and Bethanechol in children with GOR. Antacids work in the short term. Gaviscon Infant, can improve symptoms of GOR. Sulcrafate may improve symptoms.	Level I/Grade B	Review focusing on infants.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
<p>Current Pharmacological Management of Gastro-Esophageal Reflux in Children – An Evidence-Based Systematic Review (2009, Tighe, et al).</p>	<p>Systematic Review</p>	<p>Children</p>	<p>Pharmacologic management of gastroesophageal reflux.</p>	<p>Gaviscon Infant acts as a feed thickener and prevents reflux by increasing the viscosity of feeds. Should be used with caution in children at risk for dehydration. Some evidence that it is effective. There is insufficient evidence to make a recommendation regarding the role of antacids in children with GERD. Oral Ranitidine provides symptomatic relief and endoscopic improvement of esophagitis in children with GER. If the initial dose of ranitidine fails to relieve symptoms, a higher dose of ranitidine or a proton-pump inhibitor should be tried. There is evidence to support the efficacy of cimetidine in children with GERD but there are significant adverse effects. Omeprazole is effective in improvement of symptoms, pH probe findings and endoscopic findings with a good tolerability and safety profile. Omeprazole should be the first-line treatment in severe esophagitis in children. It is dose-dependent. Less data available for lansoprazole but it appears to be effective in children. Lansoprazole is dose dependent. Pantoprazole appears to be effective with limited data. Esomeprazole also has limited data but appears to be effective. There is limited efficacy of metoclopramide in children with</p>	<p>Level I/Grade A</p>	<p>Systematic review.</p>	<p>Yes</p>

			Table I	GER and significant adverse effects. There is little evidence of benefit from Domperidone but there are also no serious side effects noted. There is currently not enough evidence to draw conclusions on the use of erythromycin. No evidence exists to suggest efficacy of bethanechol in reducing GER in children. Further evidence is needed to assess the clinical benefit of sucralfate in GERD.			
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Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Controversies in the Treatment of Gastroesophageal Reflux Disease in Preterm Infants (2009, Tipnis & Tipnis).	Review Article	Preterm Infants	Review of various treatments used in the treatment of GERD	<p>Positioning: sitting exacerbates GER. Faster gastric emptying can be seen with less liquid reflux and feeding on right side followed by change to left side after 1 hour. Thickening of feeds reduces number and height of non acid reflux episodes but does not decrease acid reflux events. Continuous drip feeding reduces vomiting and reflux symptoms but chronic use of indwelling tubes that cross the gastroesophageal junction is associated with increased regurgitation and esophagitis. Oral antacids and surface agents such as alginates have been poorly studied in preterm infants. Chronic antacid use in preterm infants is not recommended. Prokinetic agents have limited role in the treatment of GERD because there is a lack of efficacy shown in the preterm population. The efficacy of bethanechol has not been determined. Erythromycin has had mixed results in improving reflux scores and feeding tolerance in preterm infants. Baclofen reduced the frequency of transient lower esophageal sphincter relaxation, decreased acid reflux, and accelerated gastric emptying in a placebo-controlled study in infants. There have been neurologic side</p>	Level I/Grade B	Review article, few studies involving preterm infants.	Yes

			Table I	<p>effects in adults. Ranitidine has been shown to protect against steroid-induced ulcers in patients who have chronic lung disease, in the preterm population. Famotidine reduced the frequency of regurgitation and at a larger dose reduced crying time in preterm infants; the pharmacokinetics and efficacy have not been studied in preterm infants. The pharmacokinetic and pharmacodynamic properties of lansoprazole and omeprazole have been studied in a very small number of neonates. Omeprazole normalized the reflux index in a small number of infants and reduced the percentage of time where the intragastric pH was less than 4 but found no difference in the frequency of reflux symptoms in the placebo and omeprazole arms at the end of treatment. An increased risk of necrotizing enterocolitis as found with chronic acid suppression. In another study, acid suppression with either H2RAs or proton pump inhibitors was associated with an increased incidence of acute gastroenteritis and community-acquired pneumonia. There are various surgical interventions that will not be addressed in this review.</p>			
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Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Multicenter, Randomized, Double-Blind Study Comparing 10, 20, and 40 mg Pantoprazole in Children (5-11 Years) with Symptomatic Gastroesophageal Reflux Disease (2006, Tolia, et al).	Randomized, double-blind, parallel group study.	Children aged 5 to 11 years with confirmed symptomatic GERD.	Treatment with Pantoprazole for symptom relief in GERD.	Pantoprazole (20 and 40 mg) is effective in reducing endoscopically proven GERD symptoms in children. Both dosages significantly reduced symptoms as early as 1 week.	Level II/Grade B	Good study design. Small sample size of 53 patients. Did not specifically address infants or neonates.	Yes/Limited
Effect of Body Position Changes on Postprandial Gastroesophageal Reflux and Gastric Emptying in the Healthy Premature Neonate (2007, Van Wijk, et al).	Randomized, cross over trial.	Healthy preterm infants, without symptoms related to GERD.	Effect of position on symptoms related to GERD, left side to right side and conversely, right side to left side.	Right lateral positioning for the first postprandial hour with a position change to the left thereafter promotes gastric emptying and reduces liquid gastroesophageal reflux in the late postprandial period.	Level II/Grade B	Very small sample size but does show promise with conservative interventions.	Yes

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Gastroesophageal Reflux: Medical Treatment (2005, Vandenplas, Y.)	Review Article	Children	Treatments for gastroesophageal reflux.	<p>Conservative therapies and reassurance are the best first approach. Prone position has lowest incidence of GER; left lateral position has intermediate incidence of GER. The prone position with head elevated 30 degrees has the lowest incidence of GER. Cornstarch as a thickening agent shows decreased esophageal acid exposure time. Prokinetic agents such as metoclopramide, domperidone and cisapride have limited efficacy. There is limited data for efficacy of erythromycin.</p> <p>There is no pediatric data for prucalopride, clobopride, or itopride. Baclofen has some limited data to support its use. Experience with antacids is limited in infants. Ranitidine and Nizatidine are not well studied in children.</p> <p>Omeprazole and lansoprazole have been best studied in children and are efficacious. Long term use of gastric acid inhibitors has been linked to bacterial overgrowth.</p>	Level I/Grade B	Review article focusing on children. Not too specific for infants and neonates.	Yes
Thickened Infant Formula Does What It Has To Do: Decrease Regurgitation (2009, Vandenplas, Y.)	Editorial comment/ Expert opinion	Infants	Use of thickening agents in the treatment of gastroesophageal reflux disease.	No outcomes noted.	Level VI/Grade D	No recommendation for use.	No

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
A Preliminary Report On the Efficacy of the Multicare AR-Bed in 3-week-3-month-old Infants On Regurgitation, Associated Symptoms and Acid Reflux (2010, Vandenplas, et al).	Prospective evaluation in an open intervention pilot study.	3-week to 3-month old infants.	Use of multicare AR (anti-reflux) bed and its effect on gastroesophageal reflux.	The 40 degree position of the incline bed decreased regurgitation in a statistically and clinically significant way.	Level III/Grade B	Very small sample size (30). Non-randomized, non controlled trial. High “drop out” rate due to infants discomfort in the inclined position.	Yes/Limited

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
The Diagnosis and Management of Gastro-oesophageal Reflux in Infants (2005, Vandenplas, et al).	Review article.	Infants.	Treatment options for gastroesophageal reflux.	<p>Table I</p> <p>Prone position has lowest incidence of GER; left lateral position has intermediate incidence of GER. The prone position with head elevated 30 degrees has the lowest incidence of GER. The risk of SIDS must be considered with positioning. Reduction in food volumes can decrease the number of regurgitations. Lifestyle changes can impact reflux. Cow's milk allergy may impact GORD, consider non cow's milk formula. Cornstarch as a thickening agent shows decreased esophageal acid exposure time. Because of nutritional concerns, commercially thickened formula is preferred to thickening agents added to formula.</p> <p>Prokinetic agents such as metoclopramide, domperidone and cisapride have limited efficacy. There is limited data for efficacy of erythromycin. There is no or very little pediatric data for ondansetron, tegaserod, prucalopride, clebopride, or itopride. Experience with antacids is limited in infants.</p> <p>Alginate-based, raft forming formulations which, in the presence of gastric acid, precipitates forming a gel, and later a foam-like pH neutral barrier in the stomach.</p> <p>Aluminum containing antacids should not be given to infants and</p>	Level I/Grade B	Review article with many older articles.	Yes

			Table I	<p>toddlers because of the nutritional and neurotoxic side effects. Sucralfate, which also contains aluminum, should not be used in infants. Ranitidine, famotidine, and Nizatidine are not well studied in children. Omeprazole and lansoprazole have been best studied in children and are efficacious. Long term use of gastric acid inhibitors has been linked to bacterial overgrowth.</p>			
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Article Title/Author	Type of Article/Study	Participants	Theme/Treatment	Outcomes	Level of Research /Grade	Study strengths/Weaknesses	Recommend for use in review
Gastroesophageal Reflux in Infancy, A Common But Challenging Presentation (2008, Weill, V).	Review Article	Infants	Treatment options for gastroesophageal reflux disease.	<p>Uncomplicated GER in infants requires time as it often resolves by the first birthday. Conservative therapy consisting of lifestyle and behavioral management would be the next line of defense. Small, more frequent feedings with frequent burping can help reduce symptoms of GER. Cow's milk protein allergy may be the cause of GER symptoms, trial of hypoallergenic formula for determination is recommended. Prone positioning decreases reflux but the risk of SIDS is of greater concern. Supine positioning is still recommended. A smoke-free environment may be beneficial for babies with reflux. Thickening agents does not reduce the acid reflux but regurgitation episodes. The acid is still there, but it cannot be seen in vomiting. Thickening of feeds can be used to treat reflux. Antacids are not recommended for long-term use. Ranitidine, famotidine, and Nizatidine are not well studied in children. Omeprazole and lansoprazole have been best studied in children and are efficacious. They are not approved for use in infants.</p>	Level I/Grade B	Yes	

Article Title/Author	Type of Article/Study	Participants	Theme/Treatment Table I	Outcomes	Level of Research /Grade	Study strengths/ Weaknesses	Recommend for use in review
Cornstarch Thickened Formula Reduces Oesophageal Acid Exposure Time in Infants (2005, Xinias, et al).	Blinded, randomized controlled trial.	Formula-fed infants with a mean age of 93 days.	Cornstarch thickened formula and its effect on gastroesophageal reflux.	A formula thickened with a specifically treated cornstarch reduces oesophageal acid exposure and reduces the frequency of clinical symptoms. In addition, the group receiving the cornstarch thickened formula had better weight gain – possibly related to decreased vomiting in part.	Level II/Grade B	Randomized controlled trial with relatively large sample size.	Yes
Age-Dependent Pharmacokinetics of Lansoprazole in Neonates and Infants (2008, Zhang, et al).	Single and repeated dose, randomized, open-label, multicenter study.	20 neonates (<28 days old) and 20 infants (>28 days but <1 year old)	Treatment with lansoprazole and the age dependent dose needed to treat gastroesophageal reflux.	The pharmacokinetics of lansoprazole are age dependent. Pediatric patients aged $\leq 10$ weeks require a lower dose of lansoprazole than pediatric patients aged $\geq 10$ weeks to achieve similar plasma exposure. Effectiveness of lansoprazole in subjects < 1 year old has not been established and was not addressed in this study.	Level II/Grade B	Good study design, small sample size.	Yes
Pharmacokinetic Properties of Esomeprazole in Children Aged 1 to 11 Years with Symptoms of Gastroesophageal Reflux Disease: A Randomized, Open-Label Study (2006, Zhao, et al)	Randomized, open label study. Uncontrolled.	Children 1 – 11 years old stratified into groups: 1-5 years and 6-11 years.	Effects of Esomeprazole of children in the treatment of gastroesophageal reflux disease.	This study shows that the pharmacokinetic properties of esomeprazole in children aged 1 to 11 years who have GERD may be both dose and age dependent. The metabolism of esomeprazole per kilogram of body weight is more rapid in younger (aged 1-5 years) children than in older (aged 6-11 years) children. Doses were well tolerated. This study did not address the effectiveness of esomeprazole.	Level II/Grade B	Randomized trial without control. Small sample size of 31 children.	Yes

## Chapter 4: Conclusions

Gastroesophageal reflux disease (GERD) is often assumed in the neonatal and infant population due to feeding intolerance and behavioral manifestations. To this day, there is no generally-agreed-upon test to determine if an infant is suffering from GERD. Unfortunately, even without diagnosis, GERD is treated frequently, especially in the hospital setting. There are not often practice guidelines for the treatment of GERD in the infant population. At the very least, it would be important to start with conservative treatments before moving towards diet changes and medications, as the evidence supports.

The majority of the articles and studies included in this systematic review focused on neonates and infants, except those studies looking at medications. There were relatively few well designed studies focusing on currently prescribed medications in the neonatal and infant populations. This can cause inappropriate dosing and perhaps prescribing of medications that are not well tolerated in infants if not well studied.

There were many studies that identified some interventions not to be efficacious. This is valuable information as it eliminates useless treatments from an approach to care. In addition, some medications that have been studied are not effective or may actually be harmful, such as cisapride.

### *Best Practice for the Treatment of Gastroesophageal Reflux*

There are evidence-based best practices for the treatment of gastroesophageal reflux disease. Initially, conservative therapies should be attempted as their side effects are minimal. Parental reassurance and education had significant results related to reducing the symptoms of gastroesophageal reflux. Symptoms of reflux diminish and even disappear over time, supporting this intervention (Orenstein & McGowan, 2008). If further treatment is warranted, there is

evidence that prone or left lateral positioning increases gastric emptying time and, therefore, decreases gastroesophageal reflux events. This positioning must be used with caution because of the risk of Sudden Infant Death Syndrome (SIDS). Cardiac monitoring must be used in conjunction with prone or left side positioning; therefore, in most cases, this intervention cannot be recommended for use in the hospital setting. One randomized crossover trial by Van Wijk, et al, (2007), showed that a right lateral position for the first hour following a feeding with a change to the left thereafter promoted gastric emptying. This had a very small sample size, but, with cardiac monitoring, could be used to decrease symptoms.

Feeding interventions can also be useful in the treatment of gastroesophageal reflux disease (GERD) and are still considered to be conservative. Smaller, more frequent feedings can decrease the symptoms of GERD. In addition, thickening of feedings can also decrease reflux episodes.

If these conservative therapies are not successful in treating GERD, there are some medications that have proven to be successful in either their acid suppression effects or their ability to increase gastric emptying times. It is important, especially with the use of pharmaceuticals, to monitor the effects of the medications and determine the continuing need for intervention.

#### *Recommendations for Future Research*

More research in the diagnosis of gastroesophageal reflux should be done so that treatment without diagnosis can be avoided. There is not a generally agreed upon “gold standard” to determine the presence of GERD. The diagnosis of GERD is made based upon symptoms such as vomiting, arching, crying, and irritability. These are vague symptoms that may be explained by another diagnosis. In addition, having an infant with GERD or suspected

GERD is stressful for families and may be expensive. It will be important in the future with stricter controls on healthcare dollars to determine true cases of GERD and treat them appropriately and to avoid treatment when GERD is not present.

*Recommended approach to the treatment of GERD*

The following is a listing of treatments from conservative to pharmacotherapy that can be used in the treatment of GERD in a stepped approach:

- Parental reassurance should be used as a first treatment as it is the easiest, least invasive treatment for infant regurgitation as symptoms usually decrease and disappear over time (Grade B).
- Prone or left-lateral positioning after feedings can reduce GERD in preterm infants but cannot be used without cardiac monitoring because of the risk of SIDS; if this is to be used as an early intervention, the patient must be continuously monitored and this must be discontinued prior to discharge home (Grade B).
- Faster gastric emptying can be seen with less liquid reflux and feeding on right side followed by change to left side after 1 hour. This approach must also include cardiac monitoring because of the risk of SIDS (Grade B).
- Small, slow, and more frequent feedings (with frequent burping) in a relaxed environment are helpful to infants with delayed gastric emptying (Grade B).
- Eliminating exposure to cow's milk (Grade B).
- Thickened feedings utilizing a commercially available product such as Enfamil AR because of the balanced nutrition in commercial products (Grade B).
- Cereal thickened formula (rice or oatmeal) can be used to reduce the frequency of regurgitation (Grade B).

- Cornstarch can be used to thicken formula if commercially available products or cereal for thickening are unsuccessful (Grade B).
- Hypoallergenic formula is supported in infants with recurrent emesis (Grade B).
- Gaviscon Infant can be used as it increases the viscosity of feeds and reduces reflux (Grade B).
- Ranitidine can be used as a first line medication treatment (Grade B).
- Omeprazole can be limitedly recommended in children under 2 years, but it is better studied in older children (Grade B).
- Lansoprazole is well tolerated in neonates and infants but its efficacy is only established in children older than 1 year (Grade B).
- Esomeprazole does have acid suppressive effects in infants older than 1 month at a dose of 1mg/kg; systemic exposure in preterm infants and neonates at a dose of 0.5mg/kg showed acid suppression but no effect on actual reflux events. Esomeprazole is only approved for use in children older than 1 year (Grade B).
- Cimetidine can be recommended limitedly for reduced regurgitation; it is not recommended for preterm infants (Grade B).

#### *Limitations to the Study*

The main limitations to this study were the ability to correlate the available studies on drug therapies done on adults to the neonatal and infant populations. Very few studies on pharmacologic agents and their efficacy in the neonatal/infant population have been completed although their use is widespread (Orenstein & Hassall, 2007). Not all review articles or studies were limited to the target population or the inclusion criteria of children up

to five years of age. It was difficult in some instances to extrapolate data for the target population.

Articles reviewed for this study demonstrated varied designs and methodologies. In many of the studies and articles reviewed, there were small sample sizes. Despite limitations to some of the studies and review articles, there are core themes that can be applied to the target population of neonates and infants.

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