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REVIEW

Management of gastroesophageal reflux disease in pediatric patients: a literature review

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Abstract: Gastroesophageal reflux (GER), defined as the passage of gastric contents into the esophagus, is a physiologic process that occurs throughout the day in healthy infants and children. Gastroesophageal reflux disease (GERD) occurs when gastric contents flow back into the esophagus and produce symptoms. The most common esophageal symptoms are vomiting and regurgitation. Lifestyle changes are the first-line therapy in both GER and GERD; medications are explicitly indicated only for patients with GERD. Surgical therapies are reserved for children with intractable symptoms or who are at risk for life-threatening complications of GERD. The laparoscopic Nissen antireflux procedure is the gold standard for the treatment of this pathology. A literature search on PubMed and Cochrane Database was conducted with regard to the management of GERD in children to provide a view of state-of-the-art treatment of GERD in pediatrics.

Keywords: gastroesophageal reflux, children, medical therapy of GERD, surgical treatment of GERD, laparoscopic Nissen procedure

Introduction

Gastroesophageal reflux (GER) is a normal physiologic process that occurs throughout the day in healthy infants, children, and adults.[1,2] GER occurs during episodes of transient relaxation of the lower esophageal sphincter or during inadequate adaptation of the sphincter tone to changes in abdominal pressure. Many episodes of reflux are short and asymptomatic, not extending above the distal esophagus.[3,4]

Gastroesophageal reflux disease (GERD), in turn, occurs when gastric contents reflux into the esophagus or oropharynx and produce symptoms.[5] In infants, GERD is considered to have a peak incidence of approximately 50% at 4 months of age and then to decline, affecting only 5%–10% of infants at 12 months of age.[5] However, the prevalence of this pathology in patients of all ages is increasing. Population-based studies suggest reflux disorders are not as common in Eastern Asia, where prevalence is 8.5%, compared with Western Europe and North America, where the current prevalence of GERD is estimated to be 10%–20%.[6]

Symptoms or conditions associated with GERD are classified as esophageal or extraesophageal. Esophageal conditions include vomiting, poor weight gain, dysphagia, abdominal or substernal/retrosternal pain, and esophagitis. Extraesophageal symptoms include respiratory symptoms, including cough and laryngitis, and dental erosions.[7] Complications of GERD that can be found on endoscopy are reflux esophagitis, peptic stricture, and rarely, Barrett esophagus and adenocarcinoma.[8] Symptoms or complications of pediatric GERD are associated with a number of typical

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clinical presentations in infants and children, depending on patient age.

Common symptoms of GERD in infants include regurgitation or vomiting associated with irritability, anorexia or feeding refusal, poor weight gain, dysphagia, presumably painful swallowing, and arching of the back during feedings. Extraesophageal symptoms are coughing, choking, wheezing, or upper respiratory symptoms. Common symptoms of GERD in children 1–5 years of age include regurgitation, vomiting, abdominal pain, anorexia, and feeding refusal without necessarily interfering with growth; however, children with clinically significant GERD or endoscopically diagnosed esophagitis may also develop an aversion to food, which can cause weight loss and malnutrition.[9]

Older children and adolescents are more likely to resemble adults in their clinical presentation with GERD and to complain of heartburn, epigastric pain, chest pain, nocturnal pain, dysphagia, and sour burps. Extraesophageal symptoms in older children can include nocturnal cough, wheezing, recurrent pneumonia, chronic sinusitis, laryngitis, or dental erosions.[10]

Diagnostic approaches

For most pediatric patients, a history and physical examination in the absence of warning signs are sufficient to reliably diagnose uncomplicated GER and initiate treatment strategies.[11] Generally speaking, diagnostic testing is not necessary.

The reliability of symptoms needed to make the clinical diagnosis of GERD is particularly high in adolescents, who often present with heartburn typical of adults. Physical examination is also essential to exclude more worrisome diagnoses that can present with reflux or vomiting (bilious vomiting, gastrointestinal tract bleeding, hepatosplenomegaly, abdominal tenderness or distension, and genetic and metabolic syndrome).[12] Nonetheless, a number of GERD symptom questionnaires have been validated and may be useful in the detection and surveillance of GERD in affected children of all age.

In infants, Orenstein's infant GER questionnaire (i-GERQ), published in 1996, may help in distinguishing GER from GERD.[13] In 2011, Kleinman et al developed another questionnaire for children that was validated for the documentation and monitoring of parent-reported GERD symptoms.[14]

Diagnostic tests must be used in a thoughtful and serial manner to document the presence of reflux of gastric contents in the esophagus, to detect complications, to establish a causal relationship between reflux and symptoms, to evaluate the efficacy of therapies, and to exclude other conditions. The choice of instrumental investigation depends on the clinical situation for which the investigation is requested.[15]

Esophageal pH monitoring or endoscopy are not necessary to confirm the presence of GER in a patient with classical symptoms of GERD. However, a pH study is required to document reflux in patients with extraesophageal symptoms such as respiratory symptoms without any GER symptoms.[16–18] Similarly, when esophagitis is suspected (pain or blood loss), upper gastrointestinal endoscopy with esophageal biopsy is recommended.[19] However, when there is some suggestion of an anatomical abnormality such as intestinal obstruction or dysphagia, a barium upper gastrointestinal series is indicated.[20,21]

The primary aims of therapy are to relieve the symptoms of patients, to promote normal weight gain and growth, to heal inflammation caused by refluxed gastric contents (esophagitis, Barrett's mucosa), and to prevent respiratory and other complications associated with chronic reflux of gastric contents.[22]

Lifestyle changes are the first-line therapy in patients with GERD. In infants, they are based on feeding changes (changing formulas, reducing feeding volume, and increasing frequency of feedings) and positioning therapy, whereas in older children and adolescents, lifestyle changes are more akin to recommendations made for adult patients, including the importance of weight loss in overweight patients, cessation of smoking, and avoiding alcohol use.[23,24]

The two major classes of pharmacologic agents for treatment of GERD are acid suppressants and prokinetic agents. The aim of acid suppressants, which act by neutralizing gastric acid, is to reduce esophageal acid exposure and thereby reduce symptoms of heartburn, alleviate esophagitis, and prevent acid-triggered respiratory symptoms.[25,26] The desired pharmacologic effects of prokinetic agents include improving contractility of the body of the esophagus, increasing lower esophageal sphincter pressure, and increasing the rate of gastric emptying.[27]

Surgical therapies are reserved for children with intractable symptoms or who are at risk for life-threatening complications of GERD. The laparoscopic Nissen antireflux procedure is actually the gold standard for the treatment of this pathology.[28]

The aim of this review is to provide an overview of GERD and to give a view of the state-of-the-art treatment of GERD in pediatrics.

Materials and methods

A literature search on PubMed and Cochrane Database was conducted with regard to management of GERD in children. The following keywords were used: "gastroesophageal reflux," "medical therapy of GERD," "surgical treatment of GERD," and "laparoscopic Nissen procedure." Sixty-five English-language studies published in the last years were considered in our study, and randomized controlled trials comparing pharmacological therapy with placebo, outcome of different treatments, or outcome of surgical treatments for children diagnosed with GERD were included.

Exclusion criteria were articles that reported outcomes in adulthood and studies published before 1990. In particular, we have analyzed randomized controlled trials, review articles, and case series about this pathology.

Surgical technique

The fundamental platform of the procedures is a limited circumferential dissection of the esophagus with a complete dissection of the esophageal hiatus and both crura, mobilization of the gastric fundus by dividing the short gastric vessels, closure of the associated hiatal defect, creation of a tensionless floppy 360° gastric wrap at the distal esophagus around an appropriately sized intraesophageal dilator limiting the wrap to no more than 2 cm, and stabilization of the wrap to the esophagus by partial-thickness bites of the esophagus during the creation of the wrap.

Results

Lifestyle changes to treat GERD in pediatrics may involve a combination of feeding changes and positioning therapy.[29] In infants, esophageal pH studies have shown that reflux is minimal in a prone position, but the risk for sudden infant death syndrome is highest in this position, and for this reason, the prone position is not recommended in infants younger than 12 months.[30] However, after infancy (>13 months), the left lateral position is found to be the best in preventing reflux because the risk for sudden infant death syndrome is greatly decreased in older age groups.[31,32]

Modifying maternal diet if infants are breast-fed, changing formulas, and reducing the feeding volume while increasing the frequency of feedings also may be effective strategies for addressing GERD in many patients.[33]

In a subset of patients (1%–10%), regurgitation may be a manifestation of a cow's milk protein allergy.[34] Therefore, a 2–4 week trial of a maternal exclusion diet that restricts at least milk and egg is recommended in breast-feeding infants with GERD symptoms, whereas an extensively hydrolyzed protein or amino acid-based formula may be appropriate in formula-fed infants.[35] In addition, in 2003, a study on formula-fed infants showed that GERD symptoms resolved in 24% of infants after a 2 week trial involving changing to a protein hydrolysate formula thickened with 1 tablespoon rice cereal, avoiding overfeeding, and sleeping in a supine position.[36] If the symptoms subside, a challenge and continuation of a milk-free diet is recommended, whereas if there is no response to hypoallergenic formula over 2–4 weeks, there is no point in continuing the formula.[36]

These recommendations are also applicable in breast-fed infants. Indeed, several studies have found that breast-fed infants may benefit from a maternal diet that restricts cow milk and eggs.[35] The feeding management strategy that involved the use of thickened feedings, either by adding up to 1 tablespoon of dry rice cereal per 1 ounce of formula or by changing to commercially thickened (added rice) formula for full-term infants who are not cow milk protein-intolerant, is a reasonable management strategy for other infants with GERD.[37]

Proton pump inhibitors (PPIs) are not recommended in this subset of patient, as only a few of the infants are likely to have acid-related causes of their symptoms, and the largest randomized controlled trial in infants showed that for symptoms presumably related to reflux disease, a PPI was not better than placebo.[38]

Lifestyle changes recommended in older children and adolescents are similar to those for adult patients, including weight loss, smoking cessation, dietary modification (avoiding caffeine, chocolate, alcohol, spicy food, carbonated beverages, and so on), and positioning changes (left lateral decubitus sleeping position with head-end elevation).[39] Different studies also have demonstrated decreased reflux episodes with postprandial chewing of sugarless gum.[40]

The two major classes of pharmacologic agents for treatment of GERD are acid suppressants and prokinetic agents. The main acid suppressants are antacids, histamine 2 receptor antagonists (H2RAs), and PPIs. The use of these medications in the treatment of pediatric GERD are similar to those in adults, other than the need to prescribe weight-adjusted doses and the need to consider the form of the drugs prescribed.

Antacid therapy is commonly used for the short-term relief of intermittent symptoms of GER in children and adolescents, but as more convenient and safe alternatives come available, chronic antacid therapy is generally not recommended.[41] Indeed, several studies link preparations containing

aluminum with aluminum toxicity and its complications in children.[42,43]

The safety and efficacy of surface-protective agents, such as alginates or sucralfate, have not been adequately studied in the pediatric population, and for this reason, no surface agent is currently recommended as an independent treatment of severe symptoms of GERD or erosive esophagitis in children.[41]

H2RAs decrease the secretion of acid by inhibiting the histamine 2 receptor on the gastric parietal cell. Randomized placebo-controlled pediatric clinic trials have shown that cimetidine and nizatidine are superior to placebo for the treatment of erosive esophagitis in children.[44] However, H2RAs have some limitations. In particular, a fairly rapid tachyphylaxis can develop within 6 weeks of initiation of treatment, limiting its potential for long-term use. In addition, it is important to recognize that cimetidine has specifically been linked to an increased risk for liver disease and gynecomastia and that these associations may be generalizable to other H2RAs.[41,45]

PPIs are the most potent class of acid suppressants. They decrease acid secretion by inhibition of H^+, K^+-ATPase in the gastric parietal cell canaliculus. Their result seems not to diminish with chronic use, and they have the capacity to maintain a gastric pH higher than 4 for a longer period than H2RAs.[46] In fact, PPIs are efficacious in patients with esophagitis refractory to high-dose H2RA therapy, and numerous randomized controlled trials in adults have demonstrated that PPIs are superior to H2RAs in relieving symptoms and healing esophagitis.[47]

In a long-term follow-up study in children, it has been shown that prolonged PPIs therapy (median, 3 years; maximum, 12 years) is safe with relatively few adverse effects.[48] Regarding the dose of PPIs in maintenance therapy, it has been shown that a full healing dose is superior to half-dose therapy.[49]

Headaches, diarrhea, constipation, and nausea have been described as occurring in up to 14% of older children and adults prescribed PPIs.[50]

One approach to acid-reducing therapy, called step-up therapy, is to start the treatment with an H2RA at standard dosage, following with a PPI at standard dosage and then a PPI at a higher dosage, if necessary, to achieve improvement. An alternative approach, called step-down therapy, is to start the treatment with a PPI at a higher dosage to achieve improvement, followed with a PPI at standard dosage and then an H2RA to maintain improvement.

Some studies have shown that therapy with an acid suppressant, such as H2RAs or IPPs, may be a risk factor for pediatric community-acquired pneumonia, gastroenteritis, candidemia, and necrotizing enterocolitis in preterm infants.[51]

The rationale for using prokinetic therapy in the treatment of GERD is based on evidence that it enhances esophageal peristalsis and accelerates gastric emptying and may have a special role in the treatment of GER in infants and children with conditions in which acid suppressants are unlikely to be helpful.

In 1999, randomized controlled trials using prolonged esophageal pH monitoring demonstrated that cisapride therapy is superior to placebo in reducing esophageal acid exposure and in enhancing esophageal acid clearance in patients with asthma or with recurrent vomiting that is adversely affecting lifestyle.[52] For the possible serious adverse events that can be associated with its use (fatal cardiac arrhythmias or sudden death), dating from July 2000 in the United States and Europe, cisapride has been restricted to a limited-access program supervised by a pediatric gastrologist. In addition, a recent study published in 2010 refuted the use of cisapride in children because it has been shown that there is no evidence that cisapride reduces symptoms of GERD.[53]

In conclusion, GERD needs profound acid suppression for a longer duration of time.

PPIs therapy is recommended for at least 12 weeks and then tapered over 2–3 months, as rebound hyperacidity is known after sudden stoppage of PPIs.[41] In a diagnosed case of GERD, if there is no symptomatic improvement in 4 weeks, then the dose of PPIs needs to be increased. If there is a relapse on withdrawal of PPIs, the medication needs to be restarted. Frequent relapses or continuous symptoms are indications for prolonged PPIs therapy or surgery.

The potential risks and benefits of successful prolonged medical therapy versus surgical therapy have not been well-studied in infants or children with various symptoms presentations, but after 5 years, surgical treatment is associated with lower total medical costs (operation, endoscopy, visits to the outpatient clinic, and medication) for chronic GERD.[54,55]

Surgical treatment

The absolute indications for GERD are apnea/near sudden infant death syndrome with GER, pneumonitis with associated lung changes, and esophagitis with ulceration or stricture. Relative indications for GERD are failure of

medical management, failure to thrive, recurrent pneumonia, atypical asthma, chronic cough, and chronic vomiting.

The laparoscopic Nissen fundoplication has largely replaced open Nissen fundoplication as the preferred operative approach in children who have normal esophageal body peristalsis.[56,57]

The literature concerning surgical treatment of GERD in children consists of a large number of descriptive papers composed by case series, but there are no published randomized controlled trials.

Many series indicating complications after antireflux surgery can be divided into intraoperative, early, and late postoperative events. Intraoperative complications, such as bleeding, bowel injury, pneumothorax, esophageal/gastric perforations, and vagal nerve injury, occur in 0.5%–11.5% of patients.[58,59] Early complications are uncommon in the initial recovery period.

The causes of persistent postoperative dysphagia include inappropriate patient selection, lack of an adequate objective preoperative evaluation, type of antireflux procedure, and technical problems with how the fundoplication was formed. Various mechanisms may cause gas bloat syndrome and, in some cases, interact to generate the syndrome; these mechanisms include abnormal motility, impaired gastric accommodation, gastric hypersensitivity, and dumping syndrome (30%).[59]

Other anatomic complications, such as disrupted (8%–12%) or slipped wrap, herniated wrap, too tight or too long fundoplication, twisted wrap, or the 2-compartment stomach, are related to technical failures and constitute unsuccessful surgery.[60]

Late events such as adhesional small-bowel obstruction (2%–10%) have lower incidence after laparoscopic fundoplication than after open fundoplication and are more common if patients undergo other concomitant procedures.[61]

Revision of the fundoplication is a reasonable approach that can be accomplished laparoscopically the first time up to 89% of the time, but this decreases to 68% for second revisions. Conversion to an open procedure was usually because of difficulties with dissection secondary to scarring or poor visualization. Laparoscopic failures requiring a redo laparoscopic procedure were associated with a failure rate of 4%, 7%, and 10%.[62]

On average, children are discharged home 1–3 days after the procedure when tolerating a soft mechanical diet, and reasonable pain control is achieved. Secondary to edema at the fundoplication, patients are maintained on a soft diet for 1 week and then gradually advanced to a regular diet at home, but there are no limitations on activity and no long-term dietary restrictions.[59–62]

Outcomes of GERD in neurologically impaired children

The severity and complications of GERD are higher and more present among neurologically impaired children. It has been shown that the prevalence of erosive esophagitis among these children is 30%–70% compared with just 5% in children without neurological defects. This group of children needs prolonged medication and needs surgery more often than children without neurological impairment.[63]

Discussion

The primary aims of therapy are to relieve the patient's symptoms, to promote normal weight gain and growth, to heal inflammation (esophagitis), and to prevent respiratory and other complications associated with chronic reflux of gastric contents. Lifestyle modifications in infants such as feeding changes and positioning therapy are useful, whereas in adolescents and older children, lifestyle modifications are similar to those of adult patients. Acid suppression remains the most effective way to relieve symptoms and to promote healing of esophagitis in patients with GERD.

It is essential to carefully follow all patients empirically treated for GERD to ensure they are improving, as there are many clinical conditions that may mimic its symptoms. A surgical approach is generally reserved for children who have persistent symptoms despite adequate medical treatment or who are at risk for life-threatening complications of GERD. The laparoscopic Nissen fundoplication has largely replaced open Nissen fundoplication as the preferred operative approach in children who have normal esophageal body peristalsis. The main benefits of the laparoscopic approach in adults and children include shorter hospital stays and fewer perioperative problems, such as prolonged ileus and respiratory infections. These procedures are safe and have similar outcomes compared with open approach; intraoperative complications such as bleeding, bowel injury, pneumothorax, esophageal/gastric perforations, and vagal nerve injury occur in 0.5%–11.5% of patients.

Persistent postoperative dysphagia includes inappropriate patient selection, shortage of an adequate objective preoperative evaluation, type of antireflux procedure, technical problem with how the fundoplication was performed, and abnormal motility. Late events such as adhesional small-bowel obstruction have lower incidence after laparoscopic

fundoplication than after open fundoplication. Revision of the fundoplication is a reasonable approach that can be accomplished laparoscopically the first time up to 89% of the time, but this decreases to 68% of the time for second revisions.

Some surgeons prefer partial fundoplication because they argue it is more physiologic, allowing venting of air from the stomach, and therefore reducing the rate of adverse effects of a total fundoplication. In addition, a partial fundoplication may be more appropriate in patients with known esophageal dysmotility, such as after esophageal atresia repair. Regardless of the technique used, there are no randomized studies comparing partial or complete fundoplication, but reports show that the efficacy and complications of partial and complete fundoplication are similar.

Recurrent GERD must be differentiated from transient symptoms because up to two-thirds of infants who undergo fundoplication can have persistent GERD-related sequelae requiring medical therapy for up to 2 months after the procedure. Wrap disruption and/or transmigration are the most common reasons for recurrent reflux. Innovation techniques for surgical treatment are laparoendoscopic single-site surgery and robot-assisted laparoscopic surgery.

Albassam et al recently published a comparative study in 50 children undergoing either a robot-assisted laparoscopic or traditional Nissen fundoplication.[64] They reported no significant differences in outcomes between both groups, and no clear benefit was perceived given the high cost associated with robotic devices. However, prospective, randomized studies in children are required to determine the real benefit and use of this novel surgical approach compared with current alternatives.

Most patients with GERD are neurologically impaired, and unfortunately, as demonstrated in a review by Vernon-Roberts et al, there are no data in the literature on the comparable risks or benefits of either treatment, and we are subsequently unable to provide recommendations on the best approach in this group of children.[65]

Conclusion

GER is common in infants, but GERD is not so common in early childhood, with a higher prevalence in neurologically impaired children. Many of infants have physiological reflux and need minimal intervention, as their symptoms resolve by 18 months of age.

Cornerstones for the optimal management of pediatric GERD include careful patient selection, a complete and thorough preoperative workup, a meticulous operation in experienced hands, and well-informed parents/caretakers.

There is no gold standard diagnostic test for GERD, but for extraesophageal manifestations and for esophagitis, pH-metry with or without impedance and endoscopy are the best investigations.

The current evidence supports the recommendation to use antisecretory therapy for the treatment of reflux esophagitis because it is very efficacious and safe, although prolonged, and in general, PPIs produce a greater reduction in acid secretion and have a longer duration of action than H2RAs.

Laparoscopic Nissen fundoplication is a safe procedure and has similar outcomes compared with an open approach, so today it is the current standard of care in the majority of patients resistant to medical therapy who are candidates for surgical treatment.

Disclosure

The authors report no conflicts of interest in this work.

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