Step-Up and Step-Down Approaches to Treatment of Gastroesophageal Reflux Disease in Children

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The single biggest change in the approach to treating pediatric gastroesophageal reflux disease (GERD) in recent years has been the empiric use of proton pump inhibitors (PPIs) for symptoms suspected to be those of GERD. In other words, PPIs have been used increasingly as a first-line concurrent diagnostic test and treatment before any investigation. Although this approach is useful for some patients, there are a number of caveats about its application to children. In general, these caveats are related to age per se (eg, infancy) and to age-related symptoms and severity of GERD itself. The most important caveats relate to the prescription of empiric PPI therapy in infants—which generally is to be avoided—and to how PPIs are used in older children—specifically, the advisability of empiric trials being of limited duration. Even in children with proven reflux esophagitis, GERD is not chronic and relapsing in all; thus, trials of therapy withdrawal are warranted. In light of many factors, including the burgeoning literature on potential risks of infections in acid-suppressed children and adults, caution with dose and duration of acid-suppressive drugs in children is urged. The role of antireflux surgery is also mentioned.

Introduction

Gastroesophageal reflux disease (GERD) in children is important because of its effect on quality of life, its chronicity into adulthood in some patients, and the nature of its complications. A basic choice in management strategy is whether to "step up" from one treatment to another or to "step down," which is the focus of this article. Before getting to the management strategies, a few areas of clarification are required. First, the terms *step up* and *step down* are defined. Then, what is to be managed is outlined (ie, reflux and reflux disease in the pediatric age group are defined). Next, risk factors for severe GERD in children and complications of GERD are discussed. Finally, the strategies themselves are addressed.

In many circumstances and for all age groups, the approach is to treat suspected GERD rather than proven GERD; in other words, a management or treatment trial is given on the basis of symptoms suggestive of GERD. Such a trial is often an indicator as to whether GERD may be the cause of symptoms.

Terminology: Step Up Versus Step Down

The terms *step up* and *step down* usually refer to therapy with acid-suppressing drugs. In this regard, the usual meaning of step up refers to starting GERD treatment with less potent acid suppression (ie, a histamine 2–receptor antagonist [H_2RA]) and moving to a more potent acid suppressor (ie, a proton pump inhibitor [PPI]) if necessary. It also could refer to a low-dose drug or a higher dose of the same drug. Step-down therapy is the reverse [1]. Step up also refers to starting with other treatment modalities (eg, lifestyle changes, prokinetics, antacids) and stepping up to acid suppression or adding another measure or drug; step down from acid suppression to these therapies is seldom performed. As antireflux surgery is part of the treatment armamentarium, its role is also addressed briefly. Because there are few pediatric data on the issue of step up versus step down, much of the discussion in this article comes from extrapolation from data in adults but with adaptation to pediatric circumstances.

Reflux and Reflux Disease in Children

Gastroesophageal reflux (GER) is a physiologic phenomenon that occurs at all ages, including in children. It is a normal occurrence postprandially. Physiologic reflux is particularly evident in infants (ie, < 12 months old), most commonly manifesting as "spitting up" or regurgitation. Spontaneous resolution occurs in 95% of infants by about 1 year of age [2,3].

GER becomes GERD when reflux is present to a greater degree quantitatively and for a sufficiently long duration (months or years) such that a complication of GER occurs. Recently, the definition of GERD in adults has been extended as follows: "GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [4]. In other words, the definition of GERD sometimes can be symptom based rather than always requiring an objectively demonstrable complication. This depends on the reliability of reporting and the likelihood that reflux of gastric contents is the cause of symptoms (ie, that the symptoms are typical of GERD). Thus, an adult who complains of heartburn, in whom the pain is assessed as likely due to reflux rather than another cause, such as myocardial disease, would be said to have GERD.

Although there is currently no consensus on applying this approach in pediatrics, it stands to reason that the approach could be applied to children, with some caveats. For example, it could apply to children who by virtue of age or developmental stage can verbalize and describe their symptoms. This would apply to most children developmentally over the age of about 6 to 8 years. One group to whom it would not apply is infants. This is not just because infants do not have the ability to verbalize symptoms. It is also because infants have a limited range of responses to stimuli. For example, crying, "irritability," arching, grunting, and grimacing are nonspecific and may be due to many causes, such as cows' milk protein intolerance, constipation, failure to "change state" ("immaturity" of the central nervous system), or so-called colic [5,6]. Because regurgitation or "spitting up" is a common occurrence in otherwise healthy infants, that they are also irritable or crying has often led to a GERD diagnosis being assumed. Nevertheless, this is more often than not a case of common but unrelated symptoms or signs being present. It is increasingly recognized that most of these are self-resolving or manageable by nonpharmacologic means [6,7••,8] and that the infants with pathologic GERD will declare themselves with time.

In all age groups, GERD is much less prevalent than GER, but this is particularly the case in infants and young children. This is in part due to the fact that some complications of GER (eg, esophageal stricture, Barrett's esophagus [BE]) are a function of severity and time. Nevertheless, GERD is increasingly recognized and occurs with greater prevalence and severity in children with certain underlying conditions.

Children at Particular Risk for Severe GERD

Children who are otherwise healthy do develop GERD that may be severe. However, severe, chronic GERD occurs more often in children with certain underlying disorders. These include neuromotor impairment, previous gastroesophageal surgery (eg, for repaired esophageal atresia or diaphragmatic hernia), and chronic lung disease (eg, cystic fibrosis) [9–14].

There are multiple proreflux mechanisms in each of these disorders [12]. One of these mechanisms is hiatal hernia, which is often overlooked in children yet is highly prevalent in severe cases of reflux (up to 40% of children with severe GERD) whether occurring in the context of one of the previously mentioned underlying disorders or in otherwise healthy children [14]. These and other related issues are discussed in greater detail elsewhere [9–14].

Complications of GER

Although nonerosive esophagitis, or nonerosive reflux disease, is probably the most prevalent form of esophagitis in children (as it is in adults), erosive esophagitis is a common complication of childhood GERD. Less common complications, such as esophageal stricture or BE, may result from severe, longstanding reflux.

BE is a metaplastic condition acquired from chronic, longstanding damage to squamous mucosa of the esophagus, which becomes replaced by columnar mucosa. This process takes time, which is why BE is seldom diagnosed in children under 10 years of age and is not described in children under 5 years of age [15,16]. Genetic factors are also a likely determinant in the development of BE, which may explain in part why only about 10% of individuals with GERD develop BE [4,17]. BE's importance is twofold: first, it is a marker for the presence of severe GERD, and second, it has a lifetime malignant potential of perhaps 6% to 10% [4,17]. The process of malignant change usually takes decades, although adenocarcinoma occasionally develops in children or young adults [18].

BE is not nearly as prevalent in children as it is in adults, but in one series of 166 children with severe endoscopically documented reflux disease requiring long-term PPI therapy, 4.8% had histologically proven BE [14]. Of the 166, 79% had one of the underlying conditions mentioned in the previous section.

Although BE traditionally has been diagnosed only if specialized intestinal-type metaplasia was present, there is a growing consensus in children and adults that cardia-type metaplasia should be included in the definition [4,19].

Symptoms are not necessarily a guide to the degree of damage associated with these different forms of injury. For example, a patient with nonerosive esophagitis may present with quite severe GERD symptoms, whereas a patient with BE may present with mild symptoms. This may be a function of chronicity, as well as esophageal and individual sensitivity.

With regard to other complications, GERD also may cause failure to thrive or dental erosions [11]. In infants with failure to thrive and symptoms of GERD, other causes of failure to thrive need to be excluded before ascribing the cause to GERD.

Less well defined is the relationship between GERD and extraesophageal disorders. Some evidence indicates that in children without neurologic defects, GERD is associated with a several-fold increase in the risk of sinusitis, laryngitis, asthma, pneumonia, and bronchiectasis [20]. One controlled study of children with persistent asthma and GERD showed that antireflux treatment significantly reduced the requirement for asthma medications [21].

The relationship between GER and apnea or apparent life-threatening events is complex and not yet fully defined. However, at present, it appears that although GER and apnea may have a temporal association or a common cause, GER is a real, but very rare, cause of apnea or apparent life-threatening events [22,23]. Conversely, apnea or apparent life-threatening events can be the cause of GER episodes [23].

Management Goals for GERD

In children, as in adults, the goals of managing GERD are to relieve symptoms, maintain symptomatic remission, heal esophagitis, treat complications, and prevent complications when possible.

It is important to determine realistic treatment goals in a given patient and not to treat in expectation of preventing a potential complication unless evidence supports such an approach. For example, in adults, there has been a trend over recent years toward the occurrence of fewer peptic strictures and less need for recurrent dilatation, although direct evidence is not yet available to indicate whether this is attributable to widespread use of acid suppression [24]. In contrast, no evidence suggests that early or more aggressive treatment of reflux disease can prevent the occurrence of BE.

Treatment

Various treatment modalities have been used for childhood GERD. Conservative, nonpharmacologic measures may be effective on their own or as adjuncts to pharmacotherapy. Options for medical therapy include antacids, prokinetics, H_2RAs, and PPIs. Various antireflux operations are in use, the most common being the Nissen fundoplication [25].

Nonpharmacologic treatment

Nonpharmacologic treatment is sometimes referred to as conservative therapy or lifestyle changes. These include measures such as weight loss [26], avoidance of smoking, avoidance of caffeine, avoidance of meals or snacks within a few hours of bedtime, and elevation of the head of the bed. The value of these approaches is well documented elsewhere [11]; they are the proper, indicated, first-line approach to individuals with GERD symptoms or adjuncts to pharmacologic treatment. Some nonpharmacologic measures are age specific or age restricted. For example, in managing infants who present with symptoms suggestive of GERD, only 2 weeks of measures that include exclusion of cows' milk, thickening of feedings, and avoidance of tobacco smoke resulted in resolution of symptoms in about one quarter of infants [7••]. Those who fail this therapy can be investigated or stepped up to pharmacotherapy.

Pharmacologic treatment

Before the mid-1970s, medical treatment for GERD largely consisted of lifestyle changes and buffering of gastric acid secretion with antacids. In the late-1970s, after clinical trials demonstrated the efficacy of cimetidine, the first H_2RA, acid suppression became the medical treatment of choice. Unfortunately, no prokinetic agents available at present show evidence of benefit in children. One medication commonly prescribed in children is metoclopramide, which often causes agitation and has been reported to cause tardive dyskinesia; therefore, its use in children is inadvisable. Oral antacids are commonly used in children for "as required" symptomatic treatment [11].

H_2RAs

An advantage of the H_2RAs is that active drug is available to block the receptor soon after absorption, usually allowing for symptom relief within 1 to 2 hours. This makes H_2RAs well suited to "on-demand" use. Another plus for these drugs is that there are pediatric data supporting the use and safety of the H_2RAs cimetidine, ranitidine, nizatidine, and famotidine in infants and children [27–30]. Cimetidine tends to be less frequently used in children, as it has more side effects than the others. A disadvantage of H_2RAs is that tolerance, or tachyphylaxis, often develops. That is, within days or weeks, the drug's effect is diminished [31,32].

PPIs

The next "step" is PPI therapy. PPIs block the final common pathway of acid secretion at the parietal cell. They also inhibit meal-induced acid secretion, whereas H_2RAs do not. By these mechanisms, PPIs offer the most potent and sustained suppression of acid secretion. Tolerance or tachyphylaxis does not occur with PPIs. Several studies have shown the efficacy and tolerability of PPIs in children [33–40]. At present, the only PPIs approved for use in children in the United States are omeprazole, lansoprazole, and (most recently) esomeprazole. None is approved for use before 1 year of age. The US Food and Drug Administration has approved omeprazole and lansoprazole for short-term (8–12 weeks) treatment of GERD in children 1 to 17 years old, whereas esomeprazole is approved for children 12 to 17 years old. These drugs result in healing of erosive esophagitis in almost all children with GERD, including those refractory to other medications and those who have failed surgery. Resolution or improvement of all GERD-related symptoms occurs. The longest-term data

Table 1. "Red flag" symptoms/signs in children

Severe symptoms
Hematemesis
Recurrent, forceful vomiting
Anemia
Dysphagia
Weight loss

are available for omeprazole, which is safe and efficacious for up to 2 years for maintaining remission of healed esophagitis [38].

Factors influencing treatment

Presenting symptoms and signs, age of child

The primary determinant of how treatment is approached is the presentation of the patient. A detailed discussion of this topic is beyond this article's scope, and the reader is referred to the NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition) GERD Guidelines, which offer a symptom-based approach to treating GERD in children [11]. That document contains one of the few mentions of step-up versus step-down approaches in children but gives no particular guidance to such, pointing out the dearth of pediatric evidence in the area. However, a few general points are worth mentioning here:

First, the presence of any "red flag" symptoms (Table 1) almost always mandates investigation rather than empiric treatment. With "red flags," if a complication of GERD is found or symptoms remain severe, PPI treatment is usually indicated.

Second, presenting symptoms and signs are often age related, and older children tend to present with more specific symptoms and symptoms more "typical" of reflux disease than do younger ones [10,11].

Nocturnal acid breakthrough

Nocturnal acid breakthrough (NAB) is a phenomenon studied relatively recently. It is defined as recovery of a gastric pH to greater than 4 for longer than 1 hour overnight in a patient receiving acid-suppression therapy [41,42•]. NAB should not be confused with reflux of acid into the esophagus or nocturnal symptoms. When they occur, nocturnal symptoms have a particularly adverse effect on quality of life [43,44]. However, many patients with NAB have no reflux of acid into the esophagus and no symptoms. NAB is of most importance in patients with severe GERD, persistent nocturnal symptoms, or BE. In most others, it is likely of little or no clinical importance. Most adult and pediatric patients taking a PPI continue to heal and have symptomatic improvement or resolution despite NAB [41,42•]. Therefore, eliminating NAB is not a necessary goal in most patients. Acid "breakthrough" is likely a good thing in most patients, as gastric acid serves several physiologic functions, including absorption of nutrients and protection from infection.

Adverse effects of acid-suppressive drugs

A growing body of evidence suggests that chronic suppression of gastric acid may have adverse effects in some children and adults. Specifically, recent data suggest that gastric acid inhibition—by PPIs or H_2RAs—may increase the risks of contracting acute gastroenteritis (odds ratio 3.58; 95% CI, 1.87–6.86) and community-acquired pneumonia (odds ratio 6.39; 95% CI, 1.38–29.70) in young children [45••]; necrotizing enterocolitis [46] and candidemia in newborns [47]; and community-acquired pneumonia [48], *Clostridium difficile* infection [49], and bacterial gastroenteritis in adults [50].

Overuse of acid-suppressive medications

Considerable potential exists for overuse of these medications, particularly in infants and young children. In fact, there is evidence that PPIs are being massively overprescribed in infancy [51••] for symptoms that likely are not due to GERD and do not warrant acid-suppressive therapy [6,8]. Treatment trials of acid suppressants are not a substitute for a thorough history and physical examination, which often reveal that a cause other than GERD is responsible for symptoms, particularly in infants [6,7••,8,11,52,53]. Constipation, milk protein allergy, and infection need to be ruled out in infants, as do other causes of symptoms that may be misinterpreted as GERD and may respond to nonpharmacologic therapy [7••], including tincture of time.

"Step up" versus "step down"

With regard to pros and cons of H_2RAs and PPIs, some factors intrinsic to the drugs are listed in Table 2.

For all age groups, there are risk–benefit and cost-effectiveness considerations regarding whether to investigate before a trial of therapy and whether to step up or step down. The data on these issues come from studies in adults [1,54–56], and although some principles are broadly applicable, there are additional factors for children, such as chronological age, age-related types of disease, and acuity and severity of symptoms, as well as risk–benefit issues particular to children. One central piece of evidence is that PPIs can serve as a cost-effective diagnostic test in certain circumstances in adults [57]. Although no pediatric data on this exist, an empiric trial of PPIs is often a sensible and useful approach in children [11]. However, there is no simple "one-size-fits-all" approach, and several caveats apply to the empiric use of PPIs in children. Although space does not permit detailed consideration of all the permutations of factors (Table 3), the major points are listed as follows.

Particular caution should be exercised when prescribing for those patients less than 6 months old. This is a basic

Table 2. Step-up (H_2RA first) vs step-down (PPI first) therapy for GERD

Factors in favor of step-up therapy
No need to use a potent drug if a less potent drug works
Less expensive up front
More potent suppression of acid has risks
Quicker onset of acid inhibition with H_2RAs than current PPIs
PPIs do not inhibit nocturnal acid breakthrough
No need to taper: less acid rebound hypersecretion than with PPIs
Liquid formulations are easily dosed per kilogram, well accepted by infants/younger children
Factors in favor of step-down therapy
Compared with H_2RAs, more potent and longer-lasting acid suppression
Highly efficacious in children and adults for the most severe GERD
Most effective drug should be used first; step-down can be cost effective
More useful than H_2RAs as diagnostic test
Adverse effects of acid suppression (eg, infections) also occur with H_2RAs
Long-term use can avoid surgery
PPIs approved for 1- to 17-year-olds (omeprazole, lansoprazole, esomeprazole) are now available in disintegrating tablet or powder formulations

GERD—gastroesophageal reflux disease; H_2RA—histamine 2–receptor antagonist; PPI—proton pump inhibitor.

Table 3. General considerations for using acid-suppression therapy in children

There is no one-size-fits-all treatment approach to pediatric patients.
Empiric trials of PPI in children less than 12 months old are seldom indicated.
PPI use in children under the age of 12 months should be done under specialist supervision. When PPIs are indicated, particular caution should be exercised, especially in children under the age of 6 months. There are few pharmacokinetic and dosing data for children under the age of 12 months.
In most patients under the age of 12 months, H_2RAs may be a better starting approach.
For patients over the age of 2–5 years or those with moderate symptoms, use of PPIs is generally the better approach.
Empiric trials of PPI may be useful if symptoms are likely those of GERD and are mild or moderate and if no "red flag" symptoms are present (see Table 1).
Empiric trials should be given for no more than 6–12 weeks; if the patient does not respond or relapses off treatment, testing may be indicated.
PPIs should not be stopped abruptly, because of acid rebound, which may cause symptoms. PPIs should be tapered, and the longer the course of PPI has been, the longer the taper.
Most patients require only a single dose of PPI given 15–30 minutes before the first meal of the day.
If patients come to endoscopy, in most cases they should be off all acid suppression for 2 weeks prior, as a partially treated patient may have few if any findings at endoscopy.
There are risks to chronic acid suppression; do not use twice-daily dosing PPI or high-dose PPI without an established need.
Patients should not be given long-term PPI therapy without a diagnosis. Even in patients with an established GERD diagnosis, trials of tapering and withdrawing medication should be given.

GERD—gastroesophageal reflux disease; H_2RA—histamine 2–receptor antagonist; PPI—proton pump inhibitor.

pediatric principle, because this is a vulnerable age group in general. More specifically for PPIs, pharmacokinetics, pharmacodynamics, and dosing in this age group are poorly understood. There are other reasons for having pause in prescribing PPIs in this age group. In the first place, there is no evidence that PPI therapy works better than placebo or conservative measures for infants with symptoms not proven to be due to GERD; second, severe GERD is unusual under the age of 1 year in the absence of an underlying pro-GERD condition (see above). Therefore, in this age group, it is prudent to reserve PPI therapy for those relatively few with severe symptoms that are due to GERD.

In addition, because acid suppression per se may have some risks, there may be some benefit to having less rather than more. Therefore, for infants with milder symptoms likely due to GERD, H_2RAs may offer some advantages over PPIs. For these reasons, empiric trials of PPI in the child less than 12 months old are seldom indicated.

In older children, empiric trials of PPIs may be given in those with mild or perhaps moderate symptoms as long as no "red flag" symptoms are present (Table 1). An important caveat is that in the absence of an established diagnosis, trials of PPI therapy should be of limited duration (~ 3 months). Even in patients in whom reflux esophagitis has been documented, intermittent trials of withdrawal of PPI therapy should be attempted [58•,59].

PPIs should not be discontinued abruptly, because rebound of acid secretion occurs, which may per se cause symptoms and give the possibly false impression that the patient has an underlying condition that requires continuous treatment [60,61]. Therefore, when PPI discontinuation is attempted, the drug should be tapered—the longer the course of PPI has been, the longer the period of taper [60].

Antireflux surgery

Surgery is an important part of the therapeutic armamentarium for reflux disease in children. It is discussed briefly here and in detail elsewhere [25]. Antireflux surgery has been a mainstay of treatment for GERD in children for 40 years. In the United States, antireflux surgery is the most common operation performed by pediatric surgeons, excluding minor procedures such as inguinal herniorrhaphy and central line placement.

However, there is increasing recognition that fundoplication has very high failure rates, especially in children with underlying neuromotor impairment, previous gastroesophageal surgery (most commonly repaired esophageal surgery or diaphragmatic hernia), or chronic respiratory disease—that is, unfortunately, in exactly those conditions that predispose children to the most severe GER (ie, who are in need of the most effective reflux control) [12,25]. Although laparoscopic antireflux surgery has a lower perioperative morbidity, it is more often accompanied by dysphagia in adults. In children, it appears to fail more often and earlier than open surgery—within 11 months, versus 17 months for open surgery [62].

Given the morbidity and failure rates of surgery, it makes sense that it be used in cases in which optimized medical therapy has failed. As PPIs can be dosed to heal esophagitis in almost all cases in children, it should be logical that surgery rates would fall. However, this does not appear to be the case. The surgical literature indicates that many children undergo surgery without reflux disease as the demonstrable cause of their symptoms/signs and without evidence of having failed optimized medical management. Very few studies report objective testing postoperatively, and those that do show high rates of failure within the first 3 years after surgery. This subject is addressed and referenced in detail elsewhere [25].

Surgery should be part of the step-up process. That is, it should be considered if optimized medical therapy fails in a patient with an established GERD diagnosis. It also should be considered when long-term PPI dependency has been demonstrated (ie, if repeated trials of medication withdrawal result in symptomatic relapse and if the patient is a good candidate for surgery) [10,25].

One circumstance that may justify a "step" directly to surgery is pulmonary aspiration of refluxed gastric contents. However, this is not a common occurrence, and it is difficult to diagnose, as history, physical examination, and special tests are not accurate for determining aspiration and cannot distinguish aspiration from below (GER) from aspiration from above (during swallowing).

Conclusions

There are safety and efficacy data in pediatrics for several H_2RAs and some PPIs. PPIs are not approved for use in children less than 1 year old and very seldom need to be used in this age group. Many disorders that are more common than GERD can cause symptoms in infants. Empiric trials of acid-suppressive medications may be given in children for short periods and with several caveats, particularly with PPIs. If patients do not respond, or if they relapse off treatment, diagnostic investigation is required before committing to longer-term treatment.

When an acid-related disorder is likely in infants, an H_2RA is probably the drug of choice for initial treatment. For moderate to severe GERD in any age group, a PPI is indicated, but pharmacokinetics and dosing have not been established below 1 year of age.

Acid-suppressive medications are overprescribed in children, especially in infants, and a growing body of evidence indicates that acid suppression with an H_2RA or PPI results in a higher rate of some infections in children. To manage the risk–benefit balance, acid-suppressive drugs should be used with caution. They also should be used in dosing quantity and frequency sufficient to treat the patient but not to make the patient achlorhydric, and not to treat in expectation of preventing some complication of GERD that may occur in the future—until there is evidence to support such practice. Antireflux surgery has a high rate of early failure in certain groups of children; therefore, discriminant patient selection for surgery is important.

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- •• Of major importance

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