# Non-Acid Gastroesophageal Reflux and Respiratory Disorders: A Literature Review[1]

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**ABSTRACT. Recent technological advances that now permit us to detect gastroesophageal reflux (GER), independent of pH, have sparked a fury of interest in non-acid GER as a potential culprit in respiratory disorders. Application of combined esophageal pH and multichannel intraluminal impedance (MII) monitoring to the study and diagnosis of GER disease (GERD) demonstrated non-acid GER to be far more frequent (in infants, children, and adults alike) than previously recognized. The following report is a review of the current literature that describes non-acid GER or that temporally associates non-acid GER with respiratory disorders.**

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## INTRODUCTION

### Persistent Respiratory Symptoms

Respiratory symptoms associated with GER have been previously described (Harding and others 1999; Wenzl and others 1999; Wenzl and others 2001; Rosen and Nurko 2004; Blondeau and others 2004). While relief of respiratory symptoms for some patients is achieved through acid suppression therapies (Meier and others 1994; Harding and others 1996; Teichtahl and others 1996), many patients continue to have respiratory symptoms that could be attributed to GER (Meier and others 1994; Harding and others 1996; Gustafsson and others 1992; Kiljander and others 1999; Garrigues and others 2003; Bowrey and others 2000). These data, in conjunction with previous studies that indicate that anti-reflux surgery produces dramatic relief of respiratory symptoms (Kennedy 1962; Overholt and Voorhees 1966; Davis and Fiuzat 1967; Skinner and Belsey 1967; Urschel and Paulson 1967; Babb and others 1970; Lomasney 1977; Henderson and Woolfe 1978; Pellegrini and others 1979), support a possible role for non-acid reflux in the persistence of respiratory symptoms following acid suppression therapy in children with acid GER.

One of the first studies linking non-acid GER with respiratory disorders came in the late 1990s when Wenzl and others (1999) reported that 88% of the total GER in infants (mean age at study, 69 ± 38 days) with either recurrent regurgitations or respiratory symptoms were non-acid. Their data also showed that, of the total GER episodes that were temporally associated with breathing irregularities, 78% were non-acid. In a later report, this same group reported a significant correlation between the time spent apneic and the time spent in reflux in the same population of infants (Wenzl and others 2001). We reported that in infants (median age at the time of study, 3 months, range 1 to 17 months) with recurrent episodes of apparent life threatening events (ALTEs) and respiratory disorders, 48% of the total GER episodes were non-acid and 41% of the episodes that were temporally associated with apnea were non-acid (Mousa and others 2005a). Rosen and Nurko (2004) reported that in children (mean age at the time of the study, 6.5 ± 5.6 years) with respiratory symptoms that include coughing, desaturations, tachypnea, wheezing, breath holding, and grunting, 45% of the total GER episodes were non-acid. Their data also indicated that respiratory symptoms within their patient population occurred significantly more often when the temporally associated GER are non-acid, mixed (both liquid and gas), and reached the proximal esophagus.

In adults, non-acid GER has been temporally associated with chronic coughing. In a study of 15 patients with chronic cough, Blondeau and others (2004) identified 7 patients who had positive symptom association probabilities (SAP) between GER and coughing. Five of the 7 (71%) had positive SAPs between non-acid GER and coughing. The authors suggest that coughing within this sub-population of chronic coughers may be induced by a component(s) of the non-acid GER or by reflux-induced esophageal distension.

Non-acid GER may also have an impact on asthma. In one of the first studies to report a correlation between asthma symptoms and esophageal acid events in asthmatics with GER, Harding and others (1999) found that 28% of asthmatics with reflux symptoms had normal esophageal pH tests. While there is currently very little data on non-acid GER and its effect(s) on the lung, anecdotal evidence suggests a possible role for non-acid GER in patients whose asthmatic symptoms were resistant to acid suppression therapy but were relieved following anti-reflux surgery (Garrigues and others 2003). A review of the literature suggests that studies employing the use of combined pH and MII techniques to test any possible link between non-acid GER and asthma are lacking.

Animal models have provided significant insight regarding the possible effects of microaspiration on increased airway reactivity secondary to reflux. Colombo and Hallberg (2000), for example, found that repeated small volume aspiration of milk (such as might occur in

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non-acid GER) in rabbits causes persistent inflammation and is associated with greater airway reactivity when compared to saline controls. Inflammation was accompanied by increased neutrophils, eosinophils, and activated (binucleate) alveolar macrophages in bronchial lavage specimens. This study supports a hypothesis for the possible role of non-acid GER in persistent respiratory symptoms and asthma via microaspiration.

**Mechanisms of Non-Acid GER-Induced Peptic Symptoms**

Due to the juxtaposition of both the trachea and the esophagus, the respiratory tract is particularly vulnerable to proximal esophageal refluxates that reach the pharynx. Two mechanisms for the pathogenesis of acid GER-induced respiratory symptoms have been proposed. The first, termed the "reflux theory," proposes that respiratory symptoms are the result of micro-aspiration of gastric contents into the lungs and/or bronchia. The second, called the "reflex theory," proposes that constriction or collapse of bronchial tubes is a vagus nerve-mediated event that follows acidification of the lower esophagus (Garrigues and others 2003).

The relatively few studies that have investigated potential mechanisms for non-acid GER-induced pathologies suggest a possible vagus nerve-mediated effect involving esophageal distension (a reflex response), a micro-aspiration effect (a reflux response), and possibly a role for a component(s) of the non-acid gastric fluid (a potential reflex and reflux response) (Rosen and Nurko 2004; Blondeau and others 2004). Regarding the later, bile acids have been proposed as a possible inflammation-promoting component of non-acid fluids. Several studies, conducted both *in vivo* and *in vitro*, demonstrate that non-acid GER containing bile has a damaging effect on esophageal and laryngeal tissues (Galli and others 2002; Shirvani and others 2000; Sung and others 2003). Wynne and others (1981) used scanning electron microscopy to show that, while mild in comparison to gastric juice or hydrochloric acid solutions at pH 1.5, cellular loss also occurs following exposure of rat tracheal mucosa to gastric juice at pH 5.9. Tobey and others (1996) used transmission electron microscopy to examine the epithelium of esophageal biopsy specimens from patients with erosive reflux, non-erosive reflux, and non-GERD controls. Their data showed that both erosive reflux and non-erosive reflux specimens contained dilated intracellular spaces whose measurements were both significantly larger than non-GERD controls. Fractionization studies involving the testing of individual gastric fluid fractions would likely facilitate identification of specific pathologic effects of different non-acid GER components.

There is a growing body of evidence to suggest that both acid and non-acid GER behave similarly and, therefore, both should be considered when attempting to correlate supraesophageal disorders with reflux (Gustafsson and others 1992; Meier and others 1994; Harding and others 1996; Kiljander and others 1999; Wenzl and others 1999; Bowrey and others 2000; Garrigues and others 2003; Rosen and Nurko 2004)

**Pathophysiology of Non-Acid Reflux**

Using combined manometry/pH/MII measurements, Sifrim and others (2001a) showed that transient lower esophageal sphincter relaxations (TLESRs) were the most common motor event underlying non-acid reflux; TLESRs accounted for 80% of non-acid GER in normal subjects and 55% of non-acid GER in symptomatic subjects.

**Proximal Migration of Non-Acid GER**

For acid GER, the proximal extent of the refluxate is considered to be risk factor for symptom generation in patients with GERD (Weusten and others 1995). Using combined pH/MII measurements, both stationary and ambulatory studies have shown that 34 to 48% of acid GER compared to 21 to 29% of non-acid GER reached the proximal esophagus (Sifrim and others 2001b; Shay and others 2004). However, in another study, Vela and others (2001) found no significant difference in the median height reached by either refluxate; 64% of acid GER and 57% of non-acid GER reached the proximal esophagus. Further investigation is required to clarify this difference in findings between the two groups.

**Esophageal Clearance of Non-Acid GER**

Esophageal volume clearance of non-acid GER is slightly faster than acid GER in adults. This difference was seen in healthy (Shay and others 2004) and in symptomatic adults (Sifrim and others 2001c). Our studies have detected no significant difference in the volume clearance of acid and non-acid GER in symptomatic children (Mousa and others 2005b).

**Frequency of Non-Acid GER**

The ratio of acid to non-acid GER fluctuates throughout the course of the day, in both control and in patients with reflux disease, as it is largely influenced by feeding. In adults, non-acid reflux is more likely to occur 30 minutes after a meal (due to the buffering effects of foods) and acid reflux occurs about an hour later (Sifrim and others 2001a). In children, non-acid reflux is more likely to occur during feeding and the first postprandial hour (Mousa and others 2005b).

The prevalence of acid and non-acid reflux has recently been tested in adults using ambulatory pH/MII monitoring. In the first study of 30 patients with symptoms of GERD and erosive esophagitis and 28 controls, both fed a standard liquid diet, Sifrim and others (2001b) found that 65% of the GER in controls was non-acid compared to 54% in symptomatic subjects. In a later study of 30 symptomatic subjects and 20 controls, both fed their normal/habitual solid-liquid meal combination, Sifrim and others (2002) found similar results; 54% of the total GER episodes in controls were non-acid compared to 38% of GER events in symptomatic subjects. In a more recent multicenter study of 60 normal volunteers who were permitted to eat their normal diet, Shay and others (2004) found that the frequency of acid reflux was twice that of the non-acid reflux. Further investigation is required to clarify these findings.

### The Ratio Between Acid and Non-acid Reflux is Influenced by Gastric Emptying

Combined pH/MII measurements have shown that while the rate of gastric emptying does not appear to influence the total number of GER episodes, it does influence the proportion of post-prandial acid and non-acid GER (Sifrim 2004). The data indicate that in adults, when the rate of gastric emptying is slow, the number of post-prandial non-acid GER episodes is higher. Conversely, when the rate of gastric emptying is fast, the number of post-prandial acid GER episodes is higher (Sifrim 2004). A study examining the impact of delayed gastric emptying on gastroesophageal reflux disease (GERD) found that the incidence of esophagitis in GERD patients with delayed gastric emptying was significantly lower than those with normal emptying (Schwizer and others 1989). This observation was explained by the protracted buffering capacity of meals in patients with slower gastric emptying (Schwizer and others 1989).

### Non-Acid GER and Peptic Symptoms

Following discontinuance of proton-pump inhibitors in patients with GERD, Vela and others (2001) found that patients reported heartburn, acid taste, and regurgitation during both acid and non-acid GER. Among the symptoms associated with non-acid GER, heartburn episodes were twice as frequent as regurgitation events. A review of the literature, with all of its contradictions, shows that the mechanism(s) by which non-acid GER induces heartburn is as yet very poorly understood (Smout 1997; Fass and Tougas 2002).

In another study, Sifrim and others (2002) found that only 12% of 200 heartburn episodes reported from among 30 patients were temporally associated with non-acid GER. Interestingly, when GERD subjects were treated with omeprazole, while acid GER was drastically decreased, the normally predominant symptom heartburn became replaced with regurgitation as the dominant symptom (Vela and others 2001).

### Treatment of Non-acid GER

The growing body evidence supporting an involvement of non-acid GER in respiratory disorders necessitates the need for development of treatment strategies aimed at either reducing the number of non-acid GER or impeding its proximal migration within the esophagus.

*Baclofen*: Studies in animals have shown that baclofen (Lehmann and others 1999, 2000; Staunton and others 2000) and other γ-amino-butyric acid ($GABA_B$) receptor agonists (Blackshaw and others 1999) are effective at reducing the number of TLESRs, the predominant mechanism for both acid and non-acid GER (Sifrim and others 2001a). In two recent studies that evaluated the effect of a $GABA_B$ receptor agonist on TLESRs in humans, baclofen was shown to effectively reduce the number of both acid and non-acid reflux events (Vela and others 2003; Koek and others 2003).

*Prokinetics*: It has been suggested that prokinetic medications might possibly have the potential to reduce the amount of non-acid reflux although to date none have been evaluated for this purpose (Rosen and Nurko 2004). They have been useful in the treatment of motility disorders in humans and in animals because they induce coordinated motility patterns. The data show that cisapride, for example, enhances antro-duodenal coordination and gastric emptying (Fraser and others 1993), stimulates propulsive motility patterns in the human jejunum (Coremans and others 1988), accelerates intestinal transit (Fraser and others 1993), and increases lower esophageal sphincter pressure (Smout and others 1985). Metoclopramide is another popular prokinetic drug that hastens stomach emptying of solid and liquid meals into the small intestines. And, like cisapride, metoclopramide increases muscle tone in the lower esophageal sphincter. Rapid emptying of meals, coupled with a tighter LES, could potentially help to decrease non-acid reflux. Anticholinergic compounds such as atropine have been shown to decrease the number of GER episodes by decreasing the number TLESRs (Lidims and others 1998), further supporting the notion that pharmacological control of reflux through control of TLESRs is possible. A review of the literature shows that prokinetics, in general, have yet to be tested for their potential effects on non-acid GER.

*Proton Pump Inhibitors*: The data show that treatment with proton pump inhibitors such as omeprazole results in a striking decrease in the amount of post-prandial acid GER with continued post-prandial regurgitation of non-acid GER. There was no significant change in the total number of post-prandial GER episodes (both acid and non-acid) following acid-suppression therapy (Vela and others 2001).

*Sodium Alginate*: While not effective at reducing the number of non-acid GER, sodium alginate appears to limit the proximal migration of reflux events so as to reduce the number of supraesophageal manifestations of GER (hoarseness, chronic cough, asthma, and so forth) (Zentilin and others 2005).

*Formula Thickening*: Thickened formula feedings is another therapeutic approach aimed at reducing the frequency and volume of regurgitation (Vandenplas and others 1998a,b; Rudolph and others 2001; Carroll and others 2002; Wenzl and others 2003). Rice cereal and bean gum are both used as thickening agents in dietary preparations. However, while rice is broken down by starch-specific enzymes in the saliva, bean gum is not and therefore maintains its thickening potential even after reaching the stomach (Vandenplas and others 1998b; Wenzl and others 2003). While not having any significant effect on the frequency of acid GER, formula thickening has been shown to reduce the number and the proximal extent of non-acid GER (Wenzl and others 2003).

*Surgical Management*: Fundoplication has been the standard surgical method for treating GER that is refractory to medical therapy. During this procedure, the fundus is gathered, wrapped, and then sutured around the LES. The resulting "plication" produces an increase in the pressure at the LES, which reduces the frequency of transient LES relaxations (Ireland and others 1993; Little 1992) and enhances gastric emptying (Hinder and

others 1989). Fundoplication reduces the frequency and volume of GER independent of the pH of the refluxate.

## SUMMARY AND CONCLUSIONS

Non-acid GER occurs considerably more often than previously recognized and is particularly frequent in patients treated with proton pump inhibitors. Non-acid GER constitutes as little as one-third and as much as two-thirds of the total daily GER among symptomatic and healthy controls.

There are preliminary data to suggest that there may be some causal relationship between non-acid GER and various respiratory disorders. As these causal relationships remain presently controversial (for example, GER and apnea in infants), further investigation is needed to confirm or reject non-acid GER as the cause of an associated disorder.

Combined pH/MII monitoring will allow investigators to obtain a more complete and thorough understanding of their patient's GER characteristics, hopefully leading to improved patient care.

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