

Gastro-Esophageal Reflux in Early Childhood Wheezers

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Summary. Wheezing is common among infants and young children due to peculiar anatomical and physiological properties of their lungs. Gastro-oesophageal reflux (GER) has been incriminated as one of the cause of non-asthmatic wheezing in this age group. The present study evaluates the magnitude of GER and its causal relationship with wheezing in early childhood. All recurrent and persistent wheezers (under two years) were investigated for GER and treated medically where tests were positive. The subjects were further profiled to identify any predictors for GER. Sixty-seven children of less than 2 years age with recurrent or persistent wheezing were evaluated for GER. Mean age of the study subjects at enrolment was 10.8 months and at onset of wheezing was 7.1 (± 3.8 S.D) months. Asthma and wheeze associated lower respiratory tract infection (WALRI) was diagnosed in about 1/3 each of the patients studied. GER studies were positive in over one-third (25/67) of cases. Forty-two percent of children who wheezed by 1 year of age had a positive GER study. Interestingly, nearly half (12/25) of the patients with an abnormal study did not have any clinical suggestion of regurgitation ("silent" GERs). The severity of wheezing was higher among those who had GER versus those who did not ($p \leq 0.048$; OR: 3.2). However, only 32% patients showed significant response to anti reflux treatment alone while others had partial response. GER, therefore, is an important cause for recurrent wheezing among children less than 2 years of age, either singularly or as a co-morbidity. The study findings justify investigations for GER among early wheezers; particularly for those who have onset of symptoms by 12 months of age or those who have severe disease. **Pediatr Pulmonol.** © 2010 Wiley-Liss, Inc.

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INTRODUCTION

Wheezing is a common illness of infant and young children due to the peculiar anatomical and physiological properties of the lung in this age group.¹ Over past few decades, it has been established that wheezing is a heterogeneous group of disorder. Most common cause of recurrent wheezing in infants and children is asthma.² But it is important to remember that "All that wheezes may not be asthma." Sporadic wheezing is more common among children and studies suggest that only less than a third of wheezy infants will develop asthma in later life.^{3,4} Gastro-esophageal reflux (GER) has also been incriminated as one of the several causes of non-asthmatic wheezing in young children and infants.⁵ GER in young infants is a complex entity by itself and is very common among infants.⁶ The spectrum of symptoms range from a totally asymptomatic ("silent" reflux) to an excessively crying and arching infant. As both wheezing as well as GER is very common in infancy the presence of GER in a wheezy child may either be causally related or else may be a mere coincidence, or may be secondary to wheezing and its medications.⁷ The patients who have "silent" GER can

be symptomatic due to wheezing.⁸ Anti-reflux treatment improves symptoms in many of these wheezing children.

To further understand, the magnitude of GER and its causal relationship with wheezing, among the early

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childhood (under 2 years of age) wheezers, the current study was conducted. All recurrent and persistent wheezers (<2 years) were investigated for GER irrespective of suggestive symptoms. We also prospectively followed up these patients for resolution of symptoms after classifying their wheeze to find how many actually benefit from anti-reflux therapy. We also analyzed the profile and clinical features of early wheezers to predict those who are more likely to have GER and should be targeted for the tests for GER (24 hr pH monitoring or gastro-esophageal scintigraphy). These are neither easily available nor inexpensive in our settings.

SUBJECTS AND METHODS

The study was conducted in the Department of Pediatrics, of a teaching hospital at New Delhi between January 2007 to March 2008. An informed consent was taken from the parents/primary care giver of the patients studied. This study had received clearance from the institution research board and ethical committee.

Study Population

Inclusion criteria: We included all the patients between 0 and 2 years of age with recurrent or persistent wheezing, as defined below:

1. The patients with more than three significant wheezing attacks within last 6 months requiring visit to hospital (out patients department [OPD]/emergency [ER]/admission) were labeled as recurrent wheezers. The patients with lesser number of episodes or less severe disease but where wheezing persisted almost daily for more than 4 weeks in the current episode were called persistent wheezers.
2. These patients should have normal/near normal chest radiographs.

Exclusion Criteria

1. Presence of pneumonia (airspace opacities on chest radiograph).
2. Extreme prematurity (children born with gestational age of <34 weeks or birth weight <1,500 g).
3. Neurological or developmental disorders.
4. Tuberculosis, chronic chest infection, Bronchiectasis.
5. Congenital heart disease.
6. Congenital anomalies related with high risk of GER like tracheo-esophageal fistula, pyloric stenosis, etc.
7. Any known allergy to oral technetium-labeled food.
8. Known or suspected immunodeficiency.

In addition to initial investigations such as complete hemogram, chest radiograph, Tuberculin skin test, and total serum IgE (normal value: male: 0–230 IU/ml;

female: 0–170 IU/ml),⁹ these patients were also investigated for GER by at least one of the following two methods. The choice of test was merely determined by availability of the test and acceptability by the parents.

Gastroesophageal Scintigraphy (GERS)

Five hundred microcurie of Technetium 99 m labeled sulphur colloid mixed with patient's milk feed was administered through nasogastric tube to avoid sticking of the tracer to the esophageal mucosa and to decrease the false positivity of the result as compared to oral administration. Serial thoraco–abdominal images were taken for a period of 1 hr at a frame rate of 30 sec per frame by using a Gamma Camera. A positive study was reported when tracer was seen refluxing into the esophagus on both cine images and on the time activity curve. The reflux was graded as distal if the tracer was seen reaching the lower one-third of esophagus and proximal if the tracer was seen in the upper two-thirds of the esophagus with or without visualization of the oropharynx.¹⁰ However, to be termed positive the reflux had to be visualized on at least two or three consecutive frames.¹¹ As the wheezing in GER may occur as a result of micro aspiration or due to esophageal-airway reflex, therefore, we considered any proximal or distal reflux as a positive test.

Ambulatory Esophageal pH Monitoring

A precalibrated glass or antimony probe with an external reference electrode was used. The probe was inserted transnasally and placed with radiological confirmation in the lower esophagus so that the pH sensitive point came to lie between the eighth and ninth dorsal vertebra. The probe measured esophageal pH during next 24 hr recording period.

Reflux index (RI), which is the percent of time spent with intra-esophageal pH <4, was used to segregate patients with physiological GER from pathological GER.¹⁰ Criteria for pathological GER was RI > 10% in infants <1 year¹² and >5% in children >1 year.¹³

All the patients were put on appropriate treatment based on their symptoms severity, recurrence rate, and investigative profile. The patients detected to have GER, by any method, were placed on anti-reflux therapy including non-pharmacological interventions like semi-prone positioning and head end elevation while sleeping and thickening of feeds. Anti-reflux medication used was Domperidone (0.1 mg/kg/dose three times a day) and Lansoprazole (15 mg once daily) for a period of 3 months.

We also classified the cases according to their disease severity at presentation as following:

- (a) Severe: The cases who were admitted earlier at least once in the wards due to wheezing were regarded as severe cases.

- (b) Moderately severe: The cases who usually needed short admission in ER and were discharged on the same day on most previous occasions.
- (c) Mild: The cases who were predominantly managed on OPD basis except occasionally for their acute problem.

All these patients were followed up for a minimum period of 3 months to assess response of respiratory symptoms to therapeutic intervention.

The study cases were then classified as:

1. Probable asthma: early wheezers who had personal or family history of atopy with or without eosinophilia; and who also had history of cough/wheeze without “colds.”
2. Wheeze-associated lower respiratory tract infection (WALRI): Early wheezers who had cough, coryza, and fever (viral prodrome) along with wheezing each time with or without a history of similar viral illness in a family member. Some of these patients who had frequent recurrence or persistent symptoms on follow-up were treated with oral or inhaled steroid.¹⁴ The steroid responders among these were finally labeled as probable asthma.
3. GER: Those cases who had a positive results by any of the GER studies and showed significant response to anti reflux measures.
4. GER plus: All those who were diagnosed and treated as GER on the basis of a positive GER study, but showed partial or poor response to anti-reflux medications.

For the purpose of our study, the patients finally labeled as probable asthma or WALRI were called GER negative group (group 1) and the cases labeled as GER and GER plus were called as GER positive group (group 2).

Statistical analysis was done using SPSS software. Data with P -value <0.05 on chi-square test were considered significant.

RESULTS

A total of 90 consecutive children <2 years of age, with recurrent or persistent wheezing were enrolled. Of these, 67 (74%) underwent investigation for GER (24 hr pH monitoring or GERS) and follow-up as per study protocol and were analyzed. Among the 23 patients not analyzed, the investigations for GER and follow-up were not available. The patient enrollment and final diagnosis is detailed in Figure 1.

In the present study, asthma was the predominant cause 34% (22/67), followed by WALRI 30% (20/67).

The prevalence of wheezing purely with GER was seen in 12% (8/67) cases. In another 25% (17/67) cases GER was associated with either WALRI or asthma. Thus, GER was a significant co-morbidity among early wheezers (37%).

Mean age of the study subjects at enrollment was 10.8 (SD ± 5.24) months (range: 3–24 m) and there were more males than females (ratio 9:2). The clinical and demographic profile of the study subjects is detailed in Table 1. Most of the patients in the study had symptoms severe enough to merit treatment after admission (severe disease 70%) or to be treated in ER (moderate disease 19%) for their management. Only few of them had received treatment predominantly on OPD basis (mild case 11%).

The mean age at onset of wheezing was lower in the Group 2 (GER positive group). While the mean frequency of attacks was almost equal at the time of enrollment among the two groups, the patients in GER positive group were more likely to have severe disease (OR: 3.2; $P = 0.048$; 95% CI = 1–11%). This group obviously had more number of patients with symptoms suggestive of reflux.

The children in group 1 with wheezing due to causes other than GER were more likely to be not exclusively breast-fed. No other feature was useful as a discriminant between those with GER (group 2) vis-a-vis those without it (group 1).

Almost all (18/19), 95% of patients who had history suggestive of reflux also had early onset of wheezing (before 1 year of age). Nearly three-fourth of these (15/19) had onset of wheezing by 6 months of age. There is a statistical significant decreasing trend ($P = 0.001$) of cases with suggestive symptomatology with increasing age, in the first 2 years of life (Table 2).

In group 2 where GER studies were positive, nearly two-third (16/25) of these children had onset of wheezing by 6 months of age and only 8% (2/25) of children had onset of wheezing after 1 year (Table 3).

The history suggestive of reflux was not concordant with a positive GER study as about one-third of cases with suggestive symptoms could not be confirmed by any of the method. Importantly, nearly half (12/25) of the patients who were found to have an abnormal study did not have any history of regurgitation—the “silent GERs” (Table 4).

Nearly 58% of patients with “silent” GER (7/12) improved with treatment. Therefore, they most likely had silent GER alone as an underlying cause for wheezing. In comparison almost 85% (11/13) of the symptoms positive patients showed benefit with anti-reflux treatment. The difference between the two groups was however not significant ($P = 0.20$).

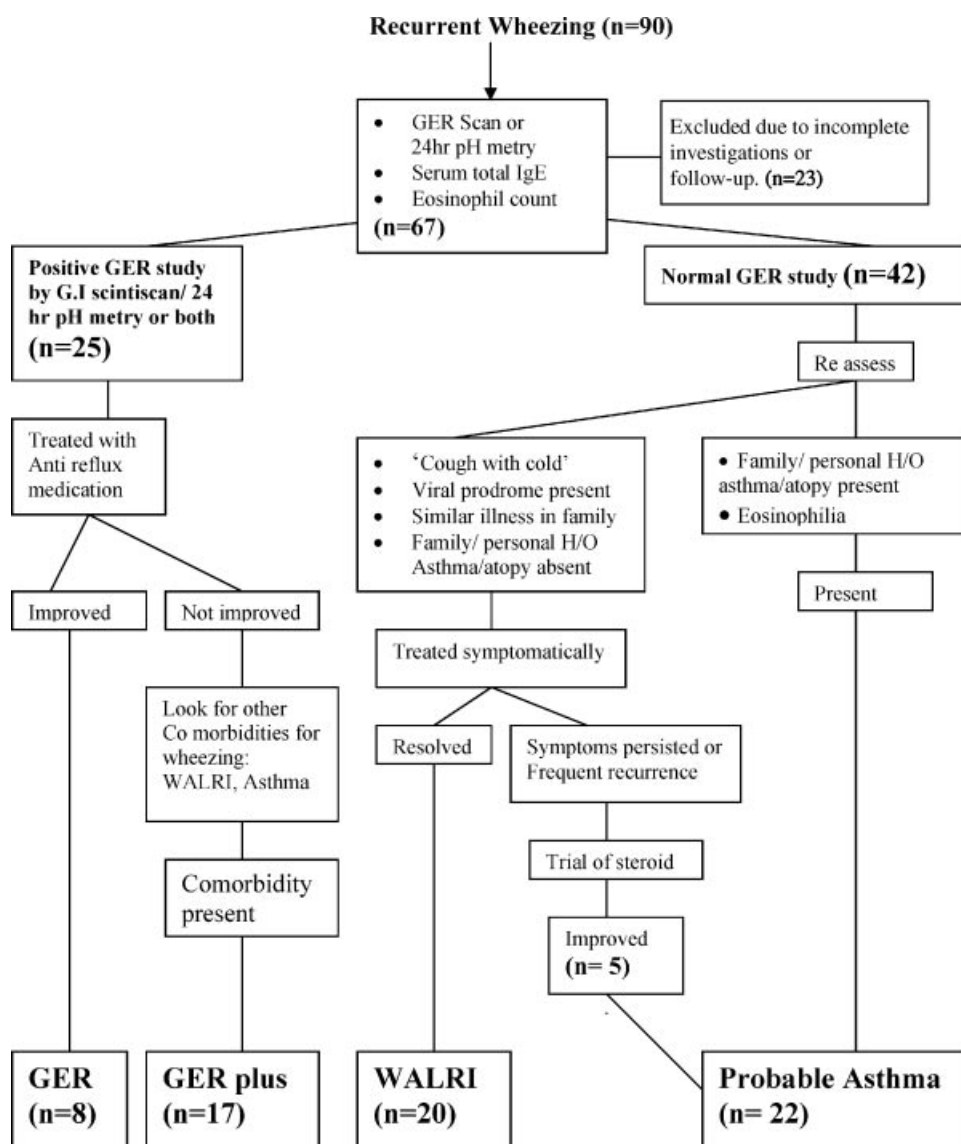


Fig. 1. Enrollment and diagnostic algorithm.

TABLE 1— Comparison of the Various Clinic-Investigative Profiles Between the Cases Who Have Positive GER Study With Those Patients With Negative GER Study (n = 67)

Clinico-investigative profile	GER positive (n = 25)	GER negative (n = 42)	P-value/odd ratio (OR)
Mean age	10.2 month	11.14 month	$P \leq 0.001$
Sex composition (M:F)	M:F = 18:7 (2.6:1)	M:F = 37:5 (7.4:1)	$P \leq 0.001$
Mean age at onset	5.9 month	7.7 month	$P \leq 0.001$
Suggestive history of reflux	13	6	OR: 6.5; $P = 0.001$
Personal or family history of asthma/atopy	7	10	$P = 0.459$
Severity (severe: moderately severe: mild)	21:3:1	26:10:6	OR: 3.2; $P = 0.048$
Mean frequency of attack before enrollment	4.8	4.7	$P = 0.068$
Exclusive breast feeding	15	15	$P = 0.046$
Bottle feeding	9	18	$P = 0.385$
Environmental factors	7	20	$P = 0.092$
Eosinophilia	4	12	$P = 0.193$
Increased serum total IgE	4	13	$P = 0.142$
Poor response to bronchodilator	7 (28%)	6 (14%)	$P = 0.146$

TABLE 2—Distribution of the Cases by the Presence or Absence of History Suggestive of Reflux According to the Age of Onset of Wheezing of the Patients

Age of onset of wheezing (months)	Total cases	Cases with history suggestive of reflux
0–6 m	35	15 (43%)
7–12 m	20	3 (15%)
13–24 m	12	1 (8%)
Total	67	19 (28%)

DISCUSSION

In the present study among recurrent and persistent wheezers under 2 years of age, GER alone or as a co-morbidity with other conditions (Asthma, WALRI) contributed to wheezing in 37% of patients.

Few existing studies have documented GER as an important morbidity in children with chronic or recurrent respiratory problems. Sheikh et al.¹⁵ in their study on 84 otherwise healthy infants with daily wheezing reported that 64% of these infants had positive esophageal pH studies. Karaman et al.¹⁶ from Turkey reported GER in 21% of their young wheezers but the mean age of their study subject was higher (17.4 months). Similarly, Foroutan et al.¹⁷ reported that 42% of their patients with chronic respiratory symptoms had GER.

The coexistence of asthma and GER has been variably reported earlier. Khoshoo et al. reported that GER disease (GERD) occurred in about two-thirds of their cases with asthma. They concluded that GER may simply represent a concomitant unrelated finding or it may be responsible for provoking or worsening asthma. GER could also be a byproduct of asthma itself. They, therefore, recommended that GERD should be suspected in wheezing patients who do not have any known risk factors for asthma or those who are becoming difficult to treat.⁷ Yuksel also reported that GER was significantly more common in non-atopic children with asthma-like airway disease and clinical improvement was significant after acid suppressor treatment. They also reported that 63% of their patients with recurrent pulmonary symptoms had GER.¹⁸ There are two studies from India documenting GER as a problem among children with respiratory problems. In one of these abnormal scintiscan was reported in 45% of asthmatic

TABLE 4—Relationship Between History Suggestive of GER With Positive GER Study

History suggestive of reflux	GER study		Total
	Positive	Negative	
Present	13	6	19
Absent	12	36	48
Total	25	42	

patients under 4 years of age.¹⁹ While the other study reported that 35% of their patients with persistent respiratory symptoms had GER.¹² Several authors have described the presence of GER as co-morbidity with other causes for wheezing such as asthma.²⁰

Among 8/67 of our patients, wheezing was purely attributable to GER due to their complete response to anti-reflux treatment. The rest had partial or no response to anti-reflux treatment and were found to have other underlying illness along with GER such as Asthma or WALRI.

Nelson et al.⁶ reported infantile reflux (IR) in 50% of infants younger than 3 months, in 67% of those aged between 4 and 6 months, and in 5% of those between 10 and 12 months. IR is benign spitting up of milk and is very common in early infancy.²¹ Perhaps, the symptomatic GER also follows a similar trend with age as is shown by our study. We tried to see if using the history suggestive of reflux as the starting point for investigations for GER study among early wheezers will be useful. History or symptoms suggestive of reflux shall correctly pick up only half of the (13/25) cases. “Silent” GER, thus is a very important part of the spectrum and contributes to symptoms outside the gastrointestinal system. Sheikh et al.¹⁵ similarly reported that nearly 44% of the GER cases contributing to wheezing in their study were “silent.” Eid et al.²² also found that 44% of patients with wheezing and with positive GER study to have silent GER. Another study by Buts et al.²³ reported that the overall incidence of “silent” GER among children with recurrent respiratory disorders was 41% (by esophagogram) and 61% (by pH monitoring criteria). How far the silent GER is contributing to the morbidity is difficult to say as the proportion of patients showing benefit to anti-reflux treatment didn’t differ between “silent-GER” and symptomatic GER cases.

Many authors in the past have reasoned that GER is a major contributor to severe disease or wheezing at different age groups^{15,17–19,22} hence the severity of symptom could be another clinical clue to identify those with GER. This was confirmed in our study as well as the illness was more severe among those who had GER (OR: 3.2; $P = 0.048$; 95% CI = 1–11%).

However, when we considered the lack of response to bronchodilators alone as a clue to presence of GER, it did

TABLE 3—Age of Onset of Wheezing Among Patients Who Had Positive GER Study

Age of onset of wheezing	Total cases	GER positive study
0–6 m	35	16/25 (64%)
7–12 m	20	7/25 (28%)
13–24 m	12	2/25 (8%)
Total	67	25 (37%)

not help. While almost twice the numbers of patients with GER failed to show good response to bronchodilators as compared to GER negative group, yet the difference was not statistically significant.

CONCLUSIONS

The present study identifies GER as an important cause occurring singularly or as a contributor to recurrent wheezing among children <2 years of age. Considering the severe and substantive morbidity due to GER among early wheezers, we feel justified to recommend using at least one of the two methods, that is, 24 h pH studies and GERS, among early wheezers. To further improve the yield of this strategy, we suggest prioritizing these tests for those who have onset of symptoms early in life, say by 12 months of age or those who have severe disease. There are no other clinical markers, which are strong enough to identify patients with GER among early childhood (<2 years) wheezers.

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