

## Gastroesophageal reflux in children with chronic recurrent cough

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### ABSTRACT

**Background** Gastroesophageal reflux (GER) is reported to be one of the most common causes of chronic recurrent cough (CRC). In Indonesia, so far there is no published data concerning GER in children with CRC.

**Objectives** To determine the prevalence of GER in children with CRC in general, and asthma in particular; and to describe the clinical profile associated with GER in these children.

**Methods** This was a cross sectional study on children with CRC who were investigated for GER using 24-hour esophageal pH monitoring. GER was graded based on reflux index (RI) stated in pHmetry results i.e., mild (RI=5-10%), moderate (RI>10-20%), and severe (RI>20%).

**Results** Among 48 children with CRC, GER was detected in 22 (46%) of them (mild GER in 14, moderate in 3, and severe in 5 children). In 35 children with asthma, which is the most frequent cause of CRC in our hospital, GER was detected in 15. The prevalence of GER increased parallel with the frequency of cough episodes i.e., 10/27 in children with infrequent episodes of cough, 4/10 in children with frequent episodes of cough, and 8/11 in children with persistent cough. Clinical profiles associated with GER in these children were persistent/ frequent episodes of CRC and undernutrition.

**Conclusions** The prevalence of GER in children with CRC was 46%, and in those with asthma was 15/35. The clinical profiles associated with GER are persistent/frequent episodes of CRC and undernutrition [*Paediatr Indones* 2004;44:201-205].

**Keywords:** gastroesophageal reflux, chronic cough, recurrent cough, asthma, children, prevalence, 24-hour esophageal monitoring

Children with a history of recurrent episodes of cough that persists for weeks to months are commonly seen in pediatric practice.<sup>1</sup> An interesting phenomenon which is drawing more attention currently is the relationship between gastroesophageal reflux (GER) and chronic

recurrent cough (CRC). The pathophysiological mechanism underlying GER-related cough is not fully understood, but may include microaspiration of esophageal contents into the larynx and tracheobronchial tree, or a vagally mediated esophageal-tracheobronchial reflex.<sup>2,3</sup> On the other side, GER as a consequence of asthma or prolonged cough has also been reported.<sup>4</sup>

Several authors have claimed GER as one of the most frequent causes of chronic cough, accounting for 10-40% of cases.<sup>2,5,6</sup> Most published data suggest that about 50% of children with CRC have "silent" GER.<sup>5,7</sup> Hitherto, a 24-hour esophageal pH monitoring tool, is a diagnostic test for detecting GER with best sensitivity and specificity.<sup>3,5,8</sup>

In Indonesia, so far, there has been no data about GER in children with CRC. The purposes of this study were to determine the prevalence of GER in children with CRC and to describe clinical profiles associated with GER in these children.

### Methods

This cross-sectional study was carried out at Cipto Mangunkusumo Hospital, Jakarta, from July 2002 to June 2004, and included all children of either

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sex with persistent cough beyond 2 weeks or recurrent cough with the last episode occurring within the last 3 months. This study was approved by the regional Ethics Committee, and every patient or parent gave informed consent. Forty-eight children were recruited by consecutive sampling. Children diagnosed as having chronic lung disease or other disorders which interfere with the pharyngeal clearance, were excluded from the study.

Details of factors associated with GER (age at onset of CRC, nocturnal cough, frequency of cough episodes, atopy, history of premature birth, nutritional status, dyspnea, gastrointestinal symptoms e.g., vomiting, nausea, and abdominal pain, irritability, and feeding difficulties), were obtained at the initial encounter with the authors. In this study, more than one episode of cough per month is considered frequent episodes of cough. Children with frequent episodes or persistent asthma were classified as having 'difficult to control' asthma.<sup>3,9</sup>

Subjects were subjected to 24-hour esophageal pH monitoring. Prior to each study, the pH monitoring probes were calibrated for pH 7 and pH 1 using appropriate buffer solutions. PH monitoring was performed using a portable pH recorder (Digitrapper MKII Synectics) with an attached electrode probe inserted transnasally such that its end came to lie upon 2 vertebrae above the diaphragm. The position of the probe was confirmed radiologically.

In this study, GER was defined as pathologic if the reflux index (RI) was >5% as stated on pHmetry.<sup>2,5,7</sup> Severity of GER (acid reflux) on pH monitoring was graded based on the reflux index<sup>7</sup> (Table 1).

TABLE 1. CRITERIA OF GER SEVERITY

Criteria	Reflux index
Normal	< 5
Mild GER	5-10
Moderate GER	>10-20
Severe GER	> 20

TABLE 2. PATIENTS' CHARACTERISTICS

Characteristics	CRC	CRC+GER
<b>Sex</b>		
Male	33	17
Female	15	5
<b>Age</b>		
<1 year	13	5
1-4 years	24	11
>4 years	11	6

(CRC + GER :  
Age range: 1.5 months–7 years 9 mo  
Mean age: 2 years 9 months)

### Statistical analysis

Statistical analysis was performed using SPSS 12.0. Chi-square test and risk estimate were used wherever applicable. A p value of <0.05 was regarded as statistically significant.

### Results

Forty-eight patients aged between 1.5 months and 10 years (mean age=2 years 7 months) were enrolled, consisting of 33 boys and 15 girls. Pathologic gastroesophageal reflux was detected in 22/48 (46%) children, in 17/33 boys and 5/15 girls (Table 2).

Five out of 22 subjects with GER were detected to have severe reflux, 3 moderate, and 14 mild (see Figure 1).

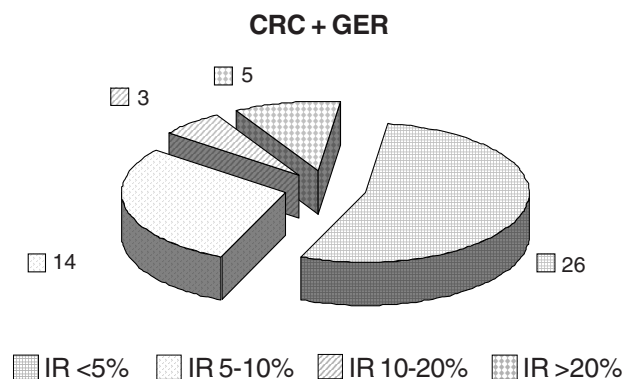


FIGURE 1. REFLUX INDEX IN CHILDREN WITH CRC

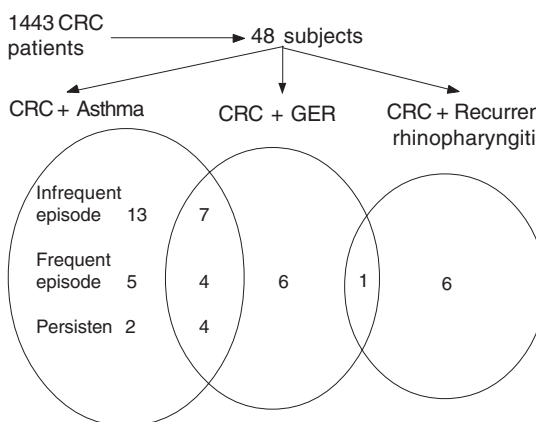


FIGURE 2. DISTRIBUTION OF SUBJECTS

**TABLE 3.** CLINICAL PROFILES OF CHILDREN WITH CRC WITH/WITHOUT PATHOLOGIC GER

Clinical profiles	GER (+)	GER (-)	Risk estimate & $\chi^2$ test
Age of onset: <1 year	14	16	PR=1.1, 95%CI 0.5;1.9, p=0.8
≥1 year	8	10	
Episode: Frequent+persistent	12	9	PR=2.0, 95%CI 1.2;3.4, p=0.05
Infrequent	10	18	
Periodicity: Nocturnal	13	17	PR=0.9, 95%CI 0.5;1.6, p=0.6
No particular period	9	9	
Atopy in the family: (+)	19	19	PR=1.7, 95%CI 0.6;4.5, p=0.2
(-)	3	7	
Premature birth: (+)	3	1	PR=1.7, 95%CI 1.0;3.4, p=0.2
(-)	19	25	
Nutritional status:			PR=2.0, 95%CI 1.1;3.2, p=0.08
Undernourished	13	9	
Well-nourished	9	17	

The clinical diagnosis of asthma was found in 35 subjects. Seven of the remaining 3 non-asthmatic children had recurrent rhinopharyngitis. Of the 35 children with asthma, pathologic GER was detected in 15 children. Pathologic GER was experienced by 7 of 20 children with infrequent episodes of asthma, 4 of 9 children with frequent episodes of asthma, and 4 of 6 children with persistent asthma (**Figure 2**). The estimated prevalence of GER in 'difficult-to-control asthma' was 8/15.

Chi-square test revealed no significant difference in the prevalence of pathologic GER between the asthma and non-asthma groups ( $p=0.4$ ,  $df=1$ ,  $PR=0.8$ , 95%CI 0.4;1.5).

Among 19 children with persistent/frequent episodes of cough, 12 were detected to have pathologic GER ( $PR=2.0$ , 95%CI 1.2;3.4,  $p=0.05$ ). The prevalence of pathologic GER increased according to the frequency of cough episodes: 10/27 in children with infrequent episodes of cough, 4/10 in frequent episodes of cough, and 8/11 in persistent cough. Thirteen out of 22 children with CRC and pathologic GER were undernourished ( $PR=2.0$ , 95%CI=1.1;3.2,  $p=0.08$ ) (**Table 3**).

The majority of subjects (44/48) with CRC had gastrointestinal symptoms. The most common symptom was vomiting, occurring in nearly all (21/22) subjects who were proven to have pathologic GER. Of 23 children with CRC who had nausea, 10 were detected to have pathologic GER. Three out of 4 subjects who experienced abdominal pain were proven to have pathological GER. Among 21 subjects who were considered irritable by the parents, 9 were detected to have pathological GER. Out of 7 subjects who had feeding difficulties (i.e., refuse to eat/drink), 5 were proven to have pathologic GER. However, none of those symptoms met statistical significance.

## Discussion

The prevalence of GER in this study was 46% among children with CRC, with male to female ratio of 3:1. Similar results were found by Vijayaratnam<sup>10</sup> who reported 44% prevalence of GER in patients with CRC, but no clear explanation is available concerning male preponderance of GER. Other investigators have observed that the airways of the male infants are

**TABLE 4.** CLINICAL MANIFESTATIONS IN CHILDREN WITH CRC WITH/ WITHOUT GER

Symptoms	GER (+)	GER (-)	Risk estimate & $\chi^2$ test
Vomiting	12	9	PR=2.0, 95%CI 0.3;10.7, p=0.3
Nausea	2	5	PR=0.9, 95%CI 0.5 ;1.7, p=0.7
Epigastric/abdominal pain	1	3	PR=1.7, 95%CI 1.0;3.3, p=0.2
Feeding difficulties	13	10	PR=1.7, 95%CI 1.0;3.1, p=0.1
Irritability	23	21	PR=0.9, 95%CI 0.5;1.7, p=0.7
Breathing difficulties	5	4	PR=1.0, 95%CI 0.4;2.2, p=0.9

Note: 1 child could have more than 1 symptoms

smaller than those of the female. It is possible that GER may be provoked by an increased expiratory effort secondary to coughing, especially in boys.<sup>11</sup> This study also observed that in the age group of 1-4 years, who are supposed to experience regurgitation rarely,<sup>12</sup> there were 11 out of 24 children detected to have pathologic GER; while in the age group of over 4 years, who normally do not have regurgitation anymore except incidentally,<sup>12</sup> pathologic GER was detected in 6 out of 11 children.

Of the 22 children with CRC who had pathologic GER, 14 were graded as having mild GER, 3 moderate, and 5 severe. A study in India (2002)<sup>7</sup> also found similar results (severe reflux cases outnumbered the moderate ones). A possible explanation for this phenomenon is that CRC is influenced by the height of reflux; the higher the reflux, the more likely it is to cause CRC.<sup>5,9</sup>

Among 48 enrolled children, 35 (73%) were diagnosed as having asthma. The prevalence of pathologic GER in children with asthma was 15/35, similar to that reported by Gastal *et al* (44%)<sup>13</sup> and Jain *et al* (40% of 40 children with CRC)<sup>7</sup>. However, this study also revealed no significant difference in the prevalence of pathological GER between the asthma and non-asthma groups. Possibly, pathologic GER is more related to CRC as a symptom, rather than to asthma as a disease.<sup>14</sup>

Gorenstein *et al*<sup>3</sup> defined 'difficult-to-control asthma' as a condition in which after 2 months of asthma treatment, a patient still suffers from frequent episodes or persistent asthma. Using that criterion, this study defined 'difficult-to-control asthma' as consisting of both frequent episodes and persistent asthma. The estimated prevalence of pathologic GER in this group was 8/15. This finding is much less than that reported by Tucci *et al* (75%)<sup>9</sup>, probably due to the smaller number of subjects in this study which indeed did not meet the sample size required to determine the prevalence of GER in children with 'difficult to control asthma'.

Several clinical profiles associated with GER were assessed in this study, including CRC onset at less than 1 year of age, frequent episodes of cough, nocturnal cough, history of premature birth, malnutrition, and gastrointestinal symptoms. Among those clinical profiles, only frequent episodes of cough and undernutrition were observed to have significant as-

sociation with GER. None of the 5 non-respiratory/gastrointestinal symptoms of GER (e.g., vomiting, nausea, epigastric/abdominal pain, feeding problems, and irritability) have any statistical significance.

This study observed the trend of increasing prevalence of pathological GER with the frequency of cough episodes i.e., 10/27 in infrequent episodes, 4/10 in frequent episodes, and 8/11 in persistent cough. Twelve of 21 children with frequent/persistent cough were detected to have pathologic GER (PR=2.0, 95%CI 1.2;3.4, and p=0.05), meaning that children with frequent/persistent CRC have a two-fold risk to have pathological GER compared to those with infrequent cough. Gorenstein *et al*<sup>3</sup> reported higher prevalence of GER in children with persistent CRC compared with those whose symptoms were easily controlled with budesonide or other nebulizer.

Pathologic GER was detected in 13 out of 22 undernourished children with CRC (PR=2.0, 95%CI 1.1;3.2, p=0.09). It means that undernourished children with CRC have a two-fold risk to have pathological GER compared to those who are well-nourished. This prevalence is much higher than that reported in developed countries (4-28%).<sup>15,16</sup>

In conclusion, this study revealed that GER prevalence in children with CRC was 46%, and in those with asthma was 15/35. Clinical profiles associated with GER were persistent/frequent episodes of CRC and undernutrition. Therefore, we recommend GER screening in children with frequent/persistent CRC and/or children with CRC who are undernourished. Further investigation about this topic is warranted, particularly since early diagnosis and prompt treatment can help the majority of the patients.

## References

1. Chang AB. Cough, cough receptors, and asthma in children. *Pediatr Pulmonol* 1999;28:59-69.
2. Kastelik JA, Jackson W, Davies TW, Wright GA, Redington AE, Wedgwood KR, *et al*. Measurement of gastric emptying in gastroesophageal reflux-related chronic cough. *Chest* 2002;122:2038-41.
3. Gorenstein A, Levine A, Boaz M, Mandelberg A, Serour F. Severity of acid gastroesophageal reflux assessed by pHmetry: is it associated with respiratory disease? *Pediatr Pulmonol* 2003;36:330-4.

4. Sontag SJ, O'Connell S, Khandelwal S. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. *Gastroenterology* 1990; 99:613-20.
5. Irwin RS, Curley FJ, French CL. Chronic cough: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis* 1990;141:640-7.
6. Juchet A, Bremont F, Dutau G, Olives JP. Chronic cough and gastroesophageal reflux in children. *Arch de Pediatri* 2001;8:629-34.
7. Jain A, Patwari AK, Bajaj P, Kashyap R, Anand VK. Association of gastroesophageal reflux disease in young children with persistent respiratory symptoms. *J Tropical Pediatr* 2002;48:39-42.
8. Mahajan L, Wyllie R, Oliva L. Reproducibility of 24-hour intraesophageal pH monitoring in pediatric patients. *Pediatrics* 1998;101:260-3.
9. Tucci F, Resti M, Fontana R, Novembre E, Lami CA, Vierucci A. Gastroesophageal reflux and bronchial asthma: prevalence and effect of therapy. *J Pediatr Gastroenterol Nutr* 1993;17:265-70.
10. Vijayaratnam V, Lin CH, Simpson P, Tolia V. Lack of significant proximal esophageal acid reflux in infants presenting with respiratory symptoms. *Pediatr Pulmonol* 1999;27:231-5.
11. Sheikh S, Stephen T, Howell L, Eid N. Gastroesophageal reflux in infants and children with chronic cough. *Pediatr Pulmonol* 1999;28:181-6.
12. Hegar B, Firmansyah A. Diagnosis refluks gastroesofagus pada anak. *Maj Kedokt Indones* 1999;49:71-5.
13. Gastal OL, Castell JA, Castell DO. Frequency and site of gastroesophageal reflux in patients with chest symptoms: studies using proximal and distal pH monitoring. *Chest* 1994;106:1793-6.
14. Vincent D, Cohen-Jonathan AM, Leport J, Merrouche M, Geronimi A, Pradalier A, et al. Gastroesophageal reflux prevalence and relationship with bronchial reactivity in asthma. *Eur Respir J* 1997;10:2255-9.
15. Clark CL, Horwitz B. Complications of gastroesophageal reflux disease. *Postgrad Med* 1996;100:95-114.
16. Shalaby TM, Orenstein SR. Efficacy of conservative therapy for infants with symptomatic gastroesophageal reflux referred by pediatricians to pediatric gastroenterologists. *J Pediatr* 2003;142:57-61.