

## Treatment Of Gastroesophageal Reflux In Children With Lipid-Laden Macrophage

*Oğuz Eğil, Memduha Sarı, Pembe Oltulu, Sevgi Pekcan*

*Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları A.B.D.*

### ABSTRACT:

#### Aim:

In chronic cough, one of the etiologies is microaspirations due to gastroesophageal reflux diseases. “Lipid-laden macrophage” (LLM) the definition of lipid-containing macrophage after staining with Sudan 4 or Oil Red O. It is considered as a sign of gastroesophageal reflux in recurrent pneumonia.

#### Materials and Methods

In this study, we retrospectively evaluated the children undergoing bronchoscopy between 2016 and 2019 in our center. Patients’ medical records have been retrospectively analyzed and their parents were called for further information.

#### Results:

261 cases underwent bronchoscopy. 72 cases were LLM positive. Of the cases: 68.6% were male (n=35) and 31.4% were female (n=16). The mean age was 5.76±0.5 years and the median age was 5.05 years. The mean and median value of lipid-laden macrophage index (LLMI) was 46.6/400 and 26/400. The lowest and highest value of LLMI were 1/400 and 320/400, respectively. 83.3% of cases suffered cough (n=60). Median duration of cough was 90 days. 19 cases required hospitalization (26.4%). The median length of hospitalization was 9 days. We idealized the medical response into 3 classes as good, moderate, poor. There was a significant relationship between gastroesophageal reflux treatment and medical response (p<0.001). Even if they were classified into 4 groups according to anti-reflux and/or inhaler remedies, the correlation continued (p<0.001). There was also a significant difference between frequency of admission and anti-reflux treatment (p<0.001).

#### Conculusion:

Based on literature and our data, we recommend prescribing anti-reflux remedy to children with pulmonary and other comorbid diseases and/or if LLMI score is too high.

*Key words: lipid-laden macrophage, gastroesophageal reflux, children*

### ÖZET:

#### Amaç:

Kronik öksürükte etyolojilerden biri gastroözofageal reflü hastalıklarına bağlı mikro aspirasyonlardır. Bronkoskopilerde “lipit yüklü makrofaj” (LYM), Sudan 4 veya Oil Red O ile boyandıktan sonra lipit içeren makrofaj tanımlanmasıdır. Tekrarlayan pnömonilerde gastroözofageal reflünün bronkoalveolar lavaj bulgusu olarak kabul edilir.

#### Gereç ve Yöntem

Bu çalışmada, merkezimizde 2016 ve 2019 yılları arasında bronkoskopi yapılan çocukları retrospektif olarak değerlendirdik. Hastaların tıbbi kayıtları geriye dönük olarak analiz edildi ve daha fazla bilgi için ebeveynleri telefonla arandı.

## Bulgular:

261 olguya bronkoskopi yapılmıştı. 72 olgu LYM pozitif idi. Vakaların% 68,6'sı erkek (n=35), %31,4'ü kız (n=16) idi. Ortalama yaş 5.76±0.5 yıl ve ortanca yaş 5.05 idi. Lipid yüklü makrofaj indeksinin (LLMI) ortalama ve ortanca değeri 46.6/400 ve 26/400 idi. En düşük ve en yüksek LLMI değeri sırasıyla 1/400 ve 320/400 idi. Vakaların %83,3'ünde öksürük vardı (n=60). Medyan öksürük süresi 9 gündü. 19 vakada hastaneye yatış gerekti (%26,4). Ortalama hastanede kalış süresi 9 gündü. Tıbbi yanıtı iyi, orta ve zayıf olarak 3 sınıfa ayırdık. Gastroözofageal reflü tedavisi ile medikal cevap arasında anlamlı ilişki vardı (p<0.001). Anti-reflü ve/veya inhaler tedavilere göre 4 gruba ayrıldığında da korelasyon devam etmiştir (p<0.001). Ayrıca başvuru sıklığı ve anti-reflü tedavisi arasında anlamlı bir fark vardı (p<0.001).

## Sonuç:

Literatür ve verilerimize dayanarak, pulmoner ve diğer komorbid hastalıkları olan çocuklara ve/veya LLMI skoru çok yüksekse, anti-reflü ilacın kullanılmasını öneriyoruz.

Anahtar kelimeler: lipit yüklü makrofaj, gastroözofageal reflü, çocuk

## INTRODUCTION

In chronic cough, one of the etiologies is chronic micro aspirations due to gastroesophageal reflux diseases (GERD). “Lipid-laden macrophage” (LLM) the definition of lipid-containing macrophage after staining with Sudan 4 or Oil Red O. It is considered as a sign of GERD in recurrent pneumonia in the bronchoalveolar lavage (BAL) fluid (*Figure 1*).

In this study, we aimed to examine the frequency of LLM in our center and its relationship with aspiration related lung diseases.

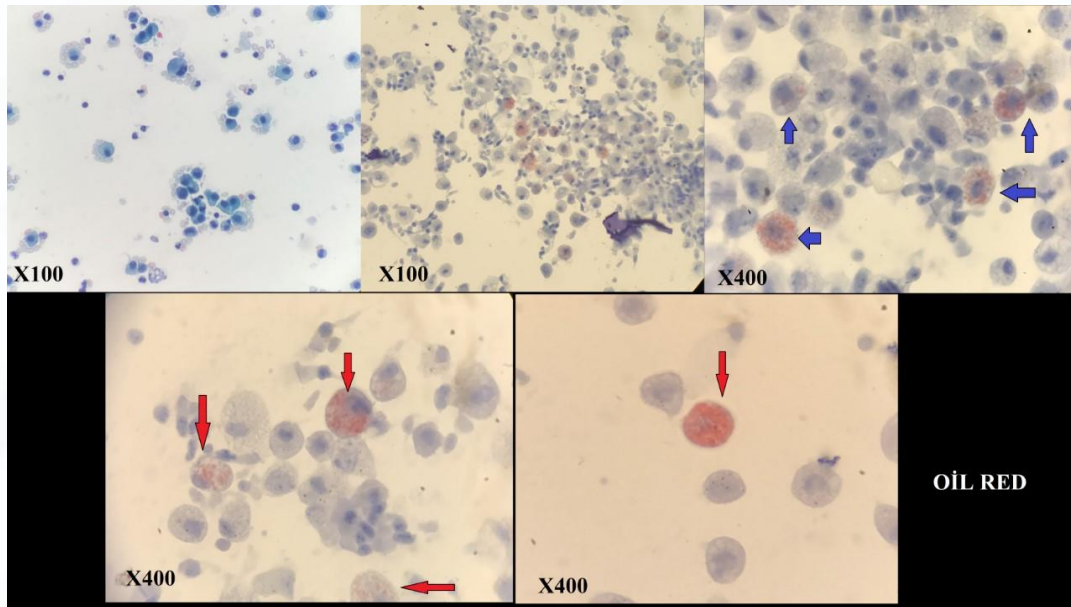


Figure 1: Pathological appearance of Lipid-laden macrophages

## MATERIALS AND METHODS

In this study, we retrospectively evaluated the children between 0-18 years who underwent bronchoscopy for any reason and ended up LLM positive between May 2016 and December 2019 in Necmettin Erbakan University Department of Pediatric Chest Diseases and reviewed

the epidemiological and clinical characteristics of them. Our inclusion criterias were being in childhood and positive for LLM. Afterwards, we reversely examined if they have cough and other clinical details.

While this study, patients' BAL pathology reports and medical records have been retrospectively analyzed and their parents were called for further medical information such as if they have cough and how long, used any anti-reflux remedy and their benefit from this treatment. Related data was analyzed in IBM SPSS 22.0 by using Chi-square, Mann Whitney U and Kruskal Wallis tests and P levels lower than 0.05 were accepted as statically significant.

## RESULTS

According to the records, a total of 261 cases underwent bronchoscopy for cough between 2016 and 2019. 72 cases were LLM positive. Of the cases: 68.6% were male (n=35) and 31.4% were female (n=16) (male/female ratio: 2.13). The mean age was  $5.76 \pm 0.5$  years and the median age was 5.05 years. Minimum and maximum age was 1 month and 17.8 years. 15.3% were younger than 1 year old (n=11). Other results are shown in *Table 1*.

Age	Frequency (n)	Percentile (%)
Lower than 1 year	11	15.3%
1-4 years (12-59 months)	25	34.7%
5-9 years (60-119 months)	24	33.3%
10-18 years (over 119 months)	12	16.7%
Total	72	100%

Table 1: Age variations of the LLM positive children

The median neutrophiles value detected in bronchoalveolar lavage was 25.0% and the median value of lymphocytes was 10.0%. The same value for macrophages was 37.5%. The mean and median value of lipid-laden macrophage index (LLMI) was 46.6/400 and 26/400 (SD=58.4). The lowest and highest value of LLMI were 1/400 and 320/400, respectively. The LLMI of 10 patients was higher than 85. Evaluating with Kruskal Wallis test, there was no correlation between value of neutrophiles and LLMI although there was a rise in neutrophiles. Other details are presented in *Table 2*.

83.3% of cases suffered cough (n=60). Chronic cough is identified as longer than 8 weeks. In this study, 47.2% of the cases had chronic cough (n=34). Mean and median duration of cough was 134.1 and 90 days (SD=123.5). The minimum and maximum duration of cough was 0 and 360 days.

19 cases required hospitalization (26.4%). The mean and median duration of hospitalization was 14.9 and 9 days (SD=20.9). The minimum and maximum duration of hospitalization was 1 and 90 days. One patient needed intensive care support that diagnosed as bronchopulmonary dysplasia due to meconium aspiration, immune deficiency and had tracheostomy. There was no mortality.

36.1% of the patients were receiving reflux treatment. Many patients having cough are thought as asthma and prescribed with inhaler remedies. In order to cease from the bias from simultaneous inhaler treatments, we also examined cases as 4 groups such as taken only anti-reflux remedy, only inhaler remedy, both of them and none. The rates of them were summarized in *Table 3*.

We idealized the medical response (to be more exact, reduce of cough) into 3 classes as good, moderate, poor and finalized according to the cases' parents' answers. There was a statistically significant relationship between receiving gastroesophageal reflux treatment and medical response ( $p < 0.001$ ). Even if they were classified into 4 groups according to anti-reflux and/or inhaler remedies which was mentioned sooner, the correlation has continued ( $p < 0.001$ ). There

was also a significant difference between frequency of admission and anti-reflux treatment ( $p<0.001$ ).

Cell Type	Mean(%)	Median(%)	St. Deviation	Minimum(%)	Maximum(%)
Neutrophiles	31.9	25.0	24.9	0	90
Lymphocytes	10.2	10.0	6.7	0	30
Macrophages	42.8	37.5	22.6	0	88
LLM	6.6	4.0	7.8	0.2	42
LLMI (/400)	46.6	26.0	58.4	1	320

Table 2: Statistical analysis of cell types in BAL

Treatment	Frequency (n)	Percentile (%)
Only anti-reflux remedy	9	12.5%
Only inhaler remedy	21	29.2%
Both of them	17	23.6%
None of them	25	34.7%
Total:	72	100%

Table 3: Patients classified according to the treatment they have taken

## DISCUSSION

In the consistent or reproductive cough, one of the etiologies is chronic microaspiration due to GERD. Lipid-laden macrophage is considered as a sign of GERD in recurrent pneumonia in the bronchoalveolar lavage (BAL) fluid. Since 1976, the relationship between GERD and chronic lung diseases such as asthma is suspected (1). In 1985, Corwin et al described LLM as a marker of aspiration in lung diseases (2) and in 1987; Colombo JL et al firstly described lipid-laden macrophage index (LLMI) and idealized the quantification (3).

LLMI did not ensure a definitive diagnosis of GERD but many early studies has shown that it is a very effective way if a patient is going to a bronchoscopy procedure for any reason (4). It doesn't mean that every GERD patient needs bronchoscopy but some GERD cases may be silent and apply with cough rather than typical reflux events or retrosternal symptoms. Many undiagnosed patient with unspecified chronic cough may be performed bronchoscopy, too. Hence, LLMI is recommended to use as an indicator of GERD in many articles (5-7)

In the literature, the mean and median age on the date of bronchoscopy usually ranges among 2-3 years old (4, 8). Differently, in our study it was 5.76 and 5.05 years, respectively. This is probably because of our patient population of having chronic diseases.

Evaluating the literature, most of the previous studies were about diagnosis process of GERD (4-6). Differently, we wanted to focus on the success of the anti-reflux treatment. While 36.1% of our patients were receiving reflux treatment, 63.9% did not. It is also notable that 18.0% of the cases (28.3% of the group without treatment) did not come to follow-ups nor show us the results of their bronchoscopy reports. (n=13).

The value of the LLMI has been approved in adult population with aspiration pneumonia (9). Nonetheless, there is an ongoing discussion whether to prescribe anti-reflux treatment to pediatric patients or not. Some articles suggested that LLMI is not an indicator for GERD (10). At the same time, many claimed the opposite (5-7). It is possible that this is due to gastroesophageal reflux has basically two main mechanisms: esophagobronchial reflex and microaspirations (6). If patient does not have the former one, he/she can't get any better naturally.

There is limited article about linking rate of LLMI and choice of treatment. De Benedictis et al suggested prescribing anti-reflux remedies if symptomatic reflux represents in pediatric asthma patients with positive LLM (7). According to Bauer ML et al, the LLMI cannot prove or disqualify aspiration independently. But high LLMI has a statistical correlation with aspiration. A positive LLMI (LLMI >85) increases the risk that a patient has clinically significant aspiration. A child who has normal growth and neurological development, and a LLMI below 85 is not likely to have clinically significant aspiration. In that article, it seems to be children with background pulmonary diseases or neurological deficiencies has more likely to have aspirations and reflux (4).

In conclusion, GERD is one of the common causes of recurrent pneumonia and chronic cough. In our study, the low rate of receiving treatment was noteworthy. Nevertheless, according to our findings, in the group with anti-reflux treatment, statistically significant success was observed. (It would be better to remind that our population in this study had many comorbid disorders.) Based on literature and our data, we recommend prescribing anti-reflux remedy to children with pulmonary, cardiac or neurological comorbid diseases and/or if LLMI score is too high. We are in thought of that studies with larger populations on children will contribute to the literature.

### Referances

- 1) Berquist WE, Rachelefsky GS, Kadden M, Siegel SC, Katz RM, Fonkalsrud EW et al. Gastroesophageal reflux-associated recurrent pneumonia and chronic asthma in children. *Pediatrics*. 1981 Jul;68(1):29-35.
- 2) Corwin RW, Irwin RS. The lipid-laden alveolar macrophage as a marker of aspiration in parenchymal lung disease. *Am Rev Respir Dis*. 1985 Sep;132(3):576-81.
- 3) Colombo JL, Hallberg TK. Recurrent aspiration in children: lipid-laden alveolar macrophage quantitation. *Pediatr Pulmonol*. 1987 Mar-Apr;3(2):86-9.
- 4) Bauer ML, Lyrene RK. Chronic aspiration in children: evaluation of the lipid-laden macrophage index. *Pediatr Pulmonol*. 1999 Aug;28(2):94-100.
- 5) Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. *Pediatr Pulmonol*. 1999 Jun;27(6):419-22.
- 6) Özdemir P, Erdiñç M, Vardar R, et al. The role of microaspiration in the pathogenesis of gastroesophageal reflux-related chronic cough. *J Neurogastroenterol Motil*. 2017;23:41–48.
- 7) de Benedictis FM, Bush A. Respiratory manifestations of gastro-oesophageal reflux in children. *Arch Dis Child*. 2018 Mar;103(3):292-296. doi: 10.1136/archdischild-2017-312890. Epub 2017 Sep 7.
- 8) Villamil M, Casas C, Restrepo SM, Caceres J, Ramirez O, Ovalle NV. Experience of Lipid Laden Macrophage Index in Bronchoalveolar Lavage in Children at a Fourth Level Children's Hospital. *Am J Respir Crit Care Med* 2019;199:A1885.
- 9) Adams R, Ruffin R, Campbell D. The value of the lipid-laden macrophage index in the assessment of aspiration pneumonia. *Aust N Z J Med* 1997;27:550-553
- 10) Rosen R, Fritz J, Nurko A, Simon D, Nurko S. Lipid-laden macrophage index is not an indicator of gastroesophageal reflux-related respiratory disease in children. *Pediatrics*. 2008 Apr;121(4):e879-84. doi: 10.1542/peds.2007-0723. Epub 2008 Mar 24.