

		ESOPHAGEAL BIOPSY		Total
		EoE-bx Positive (≥ 15/hpf)	EoE-bx Negative (< 15/hpf)	
FRACTIONAL EXHALED NITRIC OXIDE (parts per billion)	Elevated eNO (≥ 15ppb)	9 (9/18= 50%) Sensitivity	5	14
	Normal eNO (< 15ppb)	9	32 (32/37= 87%) Specificity	41 (32/41= 78%) Negative PV
Total		18	37	55

Bx = Biopsy; EoE = Eosinophilic Esophagitis; eNO = Exhaled Nitric Oxide; hpf = high power field; PV = Predictive Value; ppb = parts per billion

Fig 1. Sensitivity and specificity table of esophageal biopsy for eosinophilic esophagitis and exhaled nitric oxide.

We have shown that measurement of eNO in the normal range has a good specificity for screening out children for EoE, however, eNO is poor at identifying EoE. Testing with eNO may have clinical utility during the evaluation of EoE. When the eNO level was normal, this correctly identified more than 86% of those who did not have EoE. The measurement of eNO does not replace the required diagnostic test of an upper endoscopy with biopsy of the esophagus. Nevertheless, a normal eNO could be helpful in the approach of those EoE-suspicious children that do not have asthma, but elevated measurements were not sensitive for EoE in children. Elevated eNO levels corresponded more with respiratory airway inflammation and not with esophageal inflammation.

Limitations to our results are that this was a small pilot study in only children with suspected EoE that were referred to an allergy/immunology clinic. No children with asthma or those on PPI therapy were studied due to the confounding effect this would have on eNO. Future directions for use of eNO in EoE should be targeted to those with elevated measurements during treatment interventions.

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A case of difficult-to-treat eosinophilic asthma controlled with clarithromycin

Difficult-to-treat asthma is a major health problem that has been intensively researched. Patients with difficult-to-treat asthma have the highest incidence of hospitalizations and emergency department visits,¹ have the greatest risk of fatal asthma attacks,² and use up to 3 times more resources.³ Previous studies of patients using macrolides for 6 to 16 weeks have reported lung function and symptom improvement in asthma patients with evidence of *Chlamydia pneumoniae* or *Mycoplasma pneumoniae* infection in the upper or lower airways.⁴ Besides antibiotic effects, macrolides have anti-inflammatory and immunomodulating properties. For instance, macrolides regulate the production

of the proinflammatory cytokines tumor necrosis factor α and interleukin 8 (IL-8) by decreasing the binding of transcription factors NF- κ B and AP-1.⁵ Macrolides effectively inhibit IL-8 release and induce apoptosis in eosinophils.^{6,7} Long-term treatment with macrolides is recommended in a few lung diseases, such as diffuse panbronchiolitis, cystic fibrosis, posttransplantation bronchiolitis obliterans, and chronic obstructive pulmonary disease.^{4,8} Results from a recent randomized controlled trial demonstrated that azithromycin taken for 1 year decreased exacerbations of chronic obstructive pulmonary disease.⁸ The authors attributed these results to the antibacterial properties of this antibiotic; however, one must assume that the immunomodulatory effects of macrolides played an important role as

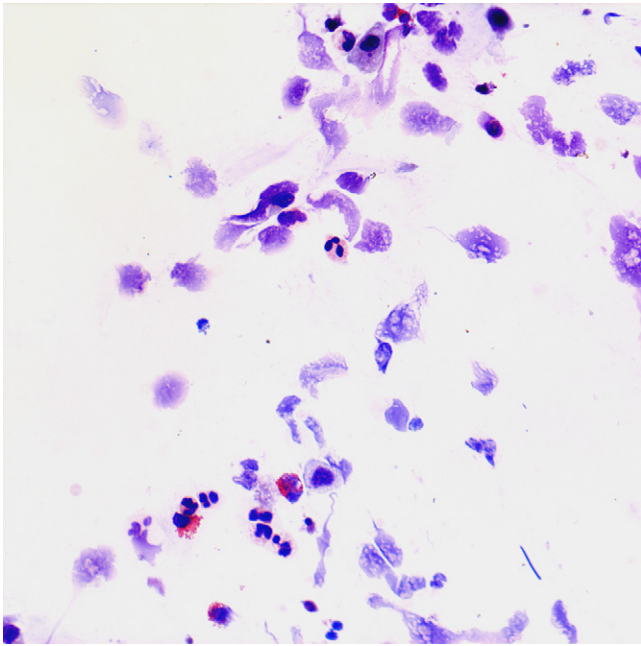


Fig 1. Initial induced sputum without prednisone showing high eosinophil count. Cytospin slide was stained with modified Wright-Giemsa, and photograph was taken at $\times 200$ magnification.

well. Until now, evidence has been insufficient to support long-term macrolide use in asthma, but it might be beneficial in a subgroup of asthma patients.

We report the case of a 61-year-old man who had late-onset chronic sinusitis with nasal polyposis in 2004, for which he underwent a polypectomy the following year, and diagnosed with asthma in 2005. He experienced uncontrolled asthma on a daily basis and severe night cough and chest tightness, which significantly impaired his life. He is a lifetime nonsmoker. Allergies were suspected after urticarial reactions to itraconazole, montelukast, azithromycin, and amoxicillin. The investigation demonstrated a mild hypogammaglobulinemia (IgG, 4.49 g/L), blood eosinophilia of 6.1%, an IgE level of 309 kU/L, normal IgM and IgA levels, negative radioallergosorbent assay results for pollens and ragweed, negative skin prick test results to common indoor aeroallergens, and negative antineutrophil cytoplasmic antibody test results. Signs of chronic sinusitis were seen on sinus computed tomogram, and rare micronodules without other abnormalities were reported on thorax high-resolution computed tomography. His forced expiratory volume in 1 second (FEV₁) was 1.74 L (52% of predicted value) with a ratio of FEV₁ to forced vital capacity of 59% during an exacerbation in January 2006, and in February 2006 a normalized FEV₁ was obtained at 3.60 L (107%). In 2006, a serologic test result for *Mycoplasma pneumonia* was positive for IgG and negative for IgM, indicating a previous infection.

Despite aggressive therapy consisting of budesonide-formoterol (200 μ g of budesonide and 6 μ g of formoterol, 4 inhalations twice daily), ciclesonide (200 μ g, 2 inhalations twice daily), tiotropium, monthly intravenous immunoglobulin, zafirlukast (20 mg twice daily), salbutamol, and sinus rinse supplemented with liquid budesonide and moxifloxacin, the patient presented repeated exacerbations up to 5 every year, requiring frequent hospitalizations, systemic corticosteroids, and antibiotics. In September 2007, omalizumab injections were initiated for local immune modulation with no improvement, and treatment was discontinued in September 2008.

In March 2008 during a follow-up visit in which the patient reported a mild asthma exacerbation, an induced sputum analysis

was performed, which revealed 12.5% of eosinophils and 53% of neutrophils (Fig. 1). After 1 month of prednisone, a marked reduction of sputum (spontaneous) eosinophils (1.75%) and neutrophils (17.5%) was observed, demonstrating corticosteroid sensitivity. The patient's condition was very well controlled with prednisone; he had no symptoms, no limitations, and a normalized FEV₁ of 3.64 L (111%). However, symptoms of asthma reappeared when decreasing or stopping prednisone therapy.

Aiming to improve asthma control and spare steroid intake, long-term daily clarithromycin (500 mg orally) was introduced in September 2009 with successful tapering of prednisone during 3 months. Long-term clarithromycin was chosen because short-term use was previously well tolerated by the patient despite a possible azithromycin allergy. The patient was able to completely stop using the prednisone and reported an adequate asthma and sinusitis control. Ciclesonide therapy was stopped, and budesonide-formoterol was decreased to 2 inhalations twice daily. Rescue medication was only required once or twice per week. During the last 2 years, he has had only one episode of sinusitis. He has had no asthma exacerbation and has not been taking prednisone since December 2009. He started again to be active. He has resumed regular activities, including bicycling and skating 3 to 4 times per week. After 26 months of clarithromycin use, induced sputum eosinophils (0.8%) and neutrophils (9.5%) remain reduced on induced sputum analysis. The patient presented with no adverse effects from his long-term use of clarithromycin.

Our case demonstrates the achievement of asthma control with daily intake of clarithromycin, which allowed the sparing of steroids. On the basis of our case, we propose that eosinophilic asthma phenotype combined with chronic sinusitis might be more responsive to long-term macrolide therapy. Long-term macrolides should be considered to optimize therapy of difficult-to-treat asthma and as a steroid-sparing drug.

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