

# Meta-analysis

## Effects of prednisone on eosinophilic bronchitis in asthma: a systematic review and meta-analysis<sup>\*,\*\*</sup>

Efeitos da prednisona na bronquite eosinofílica na asma:  
uma revisão sistemática e meta-análise

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### Abstract

**Objective:** To evaluate the effect size of oral corticosteroid treatment on eosinophilic bronchitis in asthma, through systematic review and meta-analysis. **Methods:** We systematically reviewed articles in the Medline, Cochrane Controlled Trials Register, EMBASE, and LILACS databases. We selected studies meeting the following criteria: comparing at least two groups or time points (prednisone vs. control, prednisone vs. another drug, or pre- vs. post-treatment with prednisone); and evaluating parameters before and after prednisone use, including values for sputum eosinophils, sputum eosinophil cationic protein (ECP), and sputum IL-5—with or without values for post-bronchodilator FEV<sub>1</sub>—with corresponding 95% CIs or with sufficient data for calculation. The independent variables were the use, dose, and duration of prednisone treatment. The outcomes evaluated were sputum eosinophils, IL-5, and ECP, as well as post-bronchodilator FEV<sub>1</sub>. **Results:** The pooled analysis of the pre- vs. post-treatment data revealed a significant mean reduction in sputum eosinophils (↓8.18%; 95% CI: 7.69-8.67; p < 0.001), sputum IL-5 (↓83.64 pg/mL; 95% CI: 52.45-114.83; p < 0.001), and sputum ECP (↓267.60 µg/L; 95% CI: 244.57-290.63; p < 0.0001), as well as a significant mean increase in post-bronchodilator FEV<sub>1</sub> (↑8.09%; 95% CI: 5.35-10.83; p < 0.001). **Conclusions:** In patients with moderate-to-severe eosinophilic bronchitis, treatment with prednisone caused a significant reduction in sputum eosinophil counts, as well as in the sputum levels of IL-5 and ECP. This reduction in the inflammatory response was accompanied by a significant increase in post-bronchodilator FEV<sub>1</sub>.

**Keywords:** Meta-analysis; Bronchitis; Asthma; Pulmonary eosinophilia; Evidence-based medicine; Prednisone.

### Resumo

**Objetivo:** Avaliar o tamanho do efeito do tratamento com prednisona oral na bronquite eosinofílica na asma por meio de revisão sistemática e meta-análise. **Métodos:** Revisão sistemática de artigos nas bases de dados do Medline, *Cochrane Controlled Trials Register*, EMBASE e LILACS. Foram selecionados estudos que preencheram os seguintes critérios: comparar ao menos dois grupos ou dois momentos (prednisona vs. controle, prednisona vs. outra droga ou pré vs. pós-tratamento com prednisona) e avaliar parâmetros antes e depois do uso de prednisona, incluindo eosinófilos, proteína catiônica eosinofílica (PCE) e IL-5 no escarro — com ou sem valores de VEF<sub>1</sub> pós-broncodilatador — com os IC95% correspondentes ou com dados suficientes para calculá-los. As variáveis independentes foram uso e dose de prednisona e duração do tratamento. Os desfechos avaliados foram eosinófilos, IL-5 e PCE no escarro, bem como VEF<sub>1</sub> pós-broncodilatador. **Resultados:** A análise agrupada dos dados de pré e pós-tratamento revelaram uma redução significativa nas médias de eosinófilos no escarro (↓8,18%; IC95%: 7,69-8,67; p < 0,001), IL-5 no escarro (↓83,64 pg/mL, IC95%: 52,45-114,83; p < 0,001), PCE no escarro (↓267,60 µg/L, IC95%: 244,57-290,93; p < 0,001), assim como um aumento na média de VEF<sub>1</sub> pós-broncodilatador (↑8,09%, IC95%: 5,35-10,83; p < 0,001). **Conclusões:** Em pacientes com bronquite eosinofílica de moderada a grave, o tratamento com prednisona determinou uma redução significativa nos níveis de eosinófilos no escarro, assim como nos níveis de IL-5 e PCE no escarro. Essa redução na resposta inflamatória foi acompanhada por um aumento significativo em VEF<sub>1</sub> pós-broncodilatador.

**Descritores:** Metanálise; Bronquite; Asma; Eosinofilia pulmonar; Medicina baseada em evidências; Prednisona.

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## Introduction

Eosinophilic bronchitis is a relatively new concept.<sup>(1)</sup> The term was initially used in order to define the well-known allergic inflammatory response in asthma, characterized by an elevated number of eosinophils in tissues or bronchial secretions, typically in spontaneous or induced sputum. However, eosinophilia is neither specific to nor exclusive to asthma. Eosinophilic bronchitis has been reported in association with COPD,<sup>(2)</sup> bronchiectasis,<sup>(2,3)</sup> and chronic cough, with or without asthma.<sup>(1-3)</sup> Nevertheless, eosinophilic bronchitis in asthma is relevant for various reasons: it precedes the clinical and physiological manifestations of asthma exacerbations induced by the withdrawal of corticosteroid treatment<sup>(4,5)</sup>; it has been associated with the risk of such exacerbations<sup>(4-8)</sup>; and a reduction in eosinophilia is a recognized marker of response to corticosteroid treatment.<sup>(1,9)</sup>

Predicting the response to corticosteroid treatment is relevant, particularly in asthma, because the suppression or attenuation of eosinophilic airway inflammation reduces the risk of subsequent exacerbations.<sup>(6,8,10)</sup> Systemic corticosteroids are potent anti-inflammatory drugs and the most effective therapy for suppressing airway inflammation and eosinophilia.<sup>(8,10)</sup> However, their long-term use is limited by side effects including osteoporosis, cataracts, and adrenal suppression. Currently, systemic corticosteroids are recommended to treat acute exacerbations of asthma, because they prevent the progression of exacerbations, decrease the hospitalization rate, reduce morbidity, and can be effective even when used for short periods of time.<sup>(11)</sup> They are also used as an add-on therapy to treat severe eosinophilic asthma.<sup>(9,10,12)</sup>

Only a few, small studies have examined the effectiveness of using oral corticosteroids to reduce eosinophilic airway inflammation in asthma. We therefore aimed to examine the effect size of oral corticosteroids for the treatment of airway eosinophilia in asthma patients, through systematic review and meta-analysis.

## Methods

### *Search strategy*

We searched the literature within the following electronic databases: the Cochrane Central Register

of Controlled Trials (The Cochrane Library 2007, issue 4), which contains the Acute Respiratory Infections Group's Specialized Register; Medline (1966-2012); EMBASE (1974-2012); and LILACS (1982-2012). We conducted the following searches for terms in isolation or in combination (with Boolean operators):

1. "prednisone" OR "prednisolone"
2. "asthma" OR "bronchial asthma" OR "asthma exacerbation" OR "asthma exacerbations"
3. "bronchial hyperresponsiveness" OR "bronchial hyperreactivity"
4. "cytokines"
5. "induced sputum"
6. "asthma" OR "bronchial asthma" OR "asthma exacerbation" OR "asthma exacerbations" OR "bronchial hyperresponsiveness" OR "bronchial hyperreactivity"
7. "prednisone" OR "prednisolone" AND "asthma" OR "bronchial asthma" OR "asthma exacerbation" OR "asthma exacerbations" OR "bronchial hyperresponsiveness" OR "bronchial hyperreactivity"
8. "cytokines" OR "induced sputum"
9. "prednisone" OR "prednisolone" OR "asthma" OR "bronchial asthma" OR "asthma exacerbation" OR "asthma exacerbations" OR "bronchial hyperresponsiveness" OR "bronchial hyperreactivity" AND "cytokines" OR "induced sputum"

We also searched the bibliographic references of all of the articles thus selected, even if the former had not been identified in the database search.

### *Eligibility criteria*

We initially selected articles meeting the following criteria: being a clinical trial of the effects of prednisone or prednisolone (in comparison with those of another treatment of eosinophilic bronchitis in asthma or versus a control) or a pre- and post-treatment study examining the effects of prednisone or prednisolone on eosinophilic bronchitis; involving treatment with prednisone or prednisolone for at least three days; and showing pre- and post-treatment outcomes that include sputum eosinophils, IL-5, and eosinophil cationic protein (ECP), as well as post-bronchodilator FEV<sub>1</sub>, with corresponding 95% CIs or with sufficient data for calculation. No limitations were set for participant ages or

the definition of asthma severity as used in individual studies. No unpublished or ongoing studies were included.

Two of the authors of the present study, working individually, screened the titles and abstracts of identified citations and independently acquired the full text of any article that they judged potentially eligible. They also independently reviewed and selected trials from the search results, assessing the suitability, methodology, and quality of the studies. Cases of disagreement or uncertainty were resolved by consensus or by consulting one of the other authors.

### Data extraction

We extracted the data using a protocol adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement,<sup>(13)</sup> including the study identification data; the duration of the study; the study design; inclusion and exclusion criteria; criteria for asthma diagnosis; the age and gender of the participants; the number of participants; the randomization method; the severity of asthma in the study group(s); the methods of sputum processing and measurement; and the methods of evaluating post-treatment changes in sputum eosinophils, IL-5, and ECP, as well as post-bronchodilator FEV<sub>1</sub>.

### Statistical analysis

We analyzed the data using the MIX software for meta-analysis, version 1.7 (Kitasato Clinical Research Center, Sagamihara, Japan).<sup>(14)</sup> We pooled the included studies to yield the means or medians of sputum eosinophils, ECP, IL-5, and FEV<sub>1</sub>, with the respective 95% CIs or SEs. For continuous variables, we calculated the means and 95% CIs. When the authors reported SDs, we used them to calculate SEs with the following formula:

$$SD = SE * \sqrt{(N)}$$

When the SDs were not available for these variables, we transformed 95% CIs into SDs, using the following formula:

$$SE = (\text{upper limit of 95\% CI} - \text{lower limit of 95\% CI}) / (1.96 * 2), SD = SE * \sqrt{(N)}$$

We quantified inconsistency among the pooled estimates with Higgins' I<sup>2</sup> statistic, which measures the extent of true heterogeneity and is determined as follows:

$$I^2 = [(Q - df) / Q] * 100$$

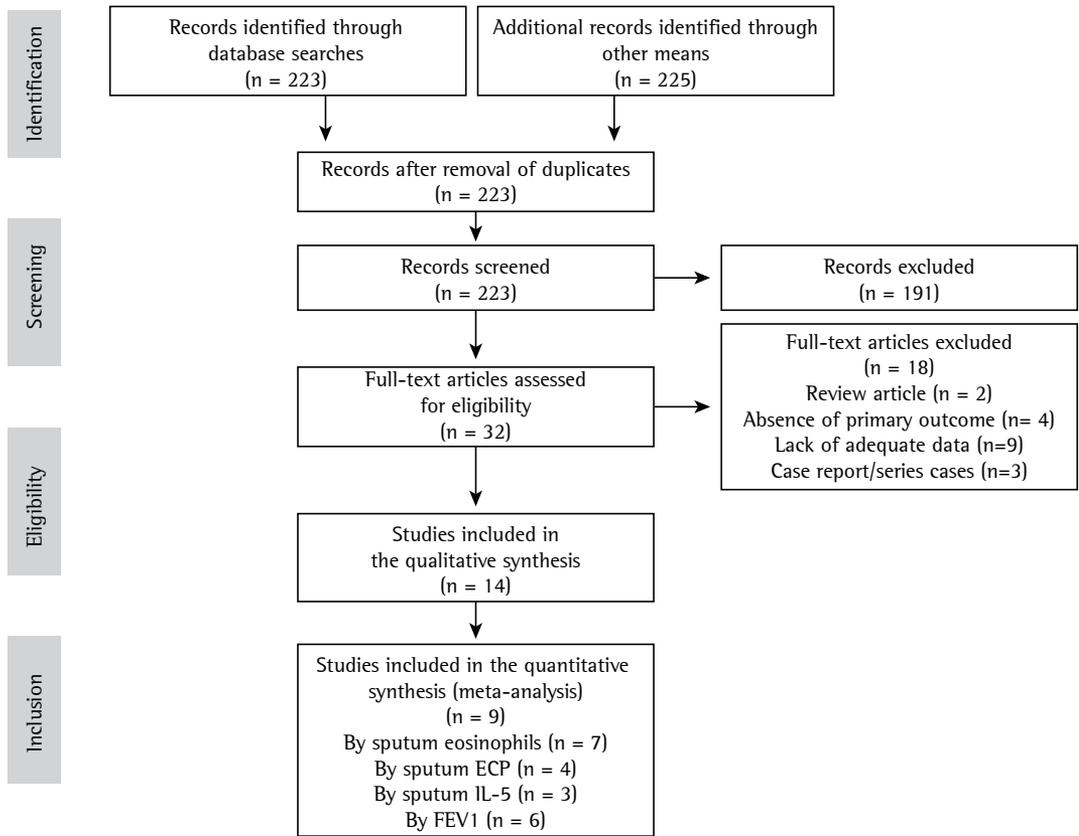
where *Q* is Cochran's *Q* (based on the chi-square statistic), and *df* is degrees of freedom. This illustrates the percentage variability in effect estimates resulting from heterogeneity rather than sampling error.<sup>(15)</sup> If heterogeneity was found, we used a random-effects model. We performed sensitivity analyses comparing random-effects and fixed-effects models. We assessed potential for publication bias using Egger's test, Higgins' I<sup>2</sup>, and funnel plots. A random-effects model was used for the analysis of sputum eosinophils, IL-5, and ECP, because of the high heterogeneity of these markers among the studies, being *Q* = 168.1; *p* < 0.001; I<sup>2</sup> = 96.4%, *Q* = 8.7; *p* = 0.013; I<sup>2</sup> = 77.0%, and *Q* = 700.9; *p* < 0.001; I<sup>2</sup> = 99.6%, respectively.

### Results

Through the database searches, we identified a total of 223 articles. Upon review of the titles and abstracts, we excluded 191 studies (Figure 1). Among the remaining 32 articles, some were further excluded: for lacking any information on primary outcomes (*n* = 4),<sup>(6,16)</sup> for being a review article or meta-analysis (*n* = 2),<sup>(17,18)</sup> for being a case report or case series (*n* = 3),<sup>(7,19,20)</sup> or for lacking adequate data for the meta-analysis (*n* = 9; evaluating a different drug, lacking a control group, or lacking pre- and post-treatment data related to the use of prednisone or prednisolone).<sup>(12,21-28)</sup> We reviewed the remaining 14 articles and found that only 8 met the inclusion criteria.<sup>(8,10,29-34)</sup> The characteristics of the included studies are presented in Table 1.

### Effects on sputum eosinophils, IL-5, and ECP

The pooled analysis (*n* = 198) showed a six-fold mean reduction in the number of sputum eosinophils after treatment (↓8.2%; 95% CI: 7.7-8.7; *p* < 0.001; Figure 2). Among studies evaluating IL-5 (in pg/mL) before and after treatment with prednisone or prednisolone (*n* = 114), there was an approximately four-fold mean decrease in IL-5 levels (↓83.6; 95% CI: 52.5-83.6; *p* < 0.001; Figure 3). In addition, among the studies evaluating ECP (in µg/L) in subjects receiving prednisone or prednisolone (*n* = 80), the treatment resulted in a five-fold



**Figure 1** – Flowchart of study selection. ECP: eosinophil cationic protein.

mean reduction in ECP levels ( $\downarrow 267.6$ ; 95% CI: 244.6–290.6;  $p < 0.001$ ; Figure 4).

### Effects on FEV<sub>1</sub>

We also analyzed changes in post-bronchodilator FEV<sub>1</sub> after treatment with prednisone or prednisolone in the 194 asthma patients for whom the relevant data were available.<sup>(8,10,29-32)</sup> In that analysis, we also used a random-effects model, because of the high heterogeneity ( $Q = 46.03$ ;  $p < 0.0001$ ;  $I^2 = 89.1\%$ ). After 6-14 days of treatment, there was a significant mean increase in post-bronchodilator FEV<sub>1</sub> ( $\uparrow 8.1\%$ ; 95% CI: 5.3-10.8;  $z = 5.8$ ;  $p < 0.001$ ; Figure 5). An analysis of the data regarding the absolute values for post-bronchodilator FEV<sub>1</sub> (in liters) showed a mean post-treatment increase, from 1.88 to 2.34 L ( $\uparrow 0.46$  L;  $p < 0.001$ ; data not shown).

### Management of results

Because of the high heterogeneity, we conducted a meta-regression to examine

the effects of treatment with prednisone or prednisolone by age, gender, and dose (Figure 6). The prednisone dose appeared to be responsible for the heterogeneity in sputum eosinophil counts ( $T^2 = 8.753$ ) and ECP ( $T^2 = 172.8$ ). Linear regression did not show an association between prednisone dose and sputum eosinophils ( $p = 0.55$ ), sputum ECP ( $p = 0.38$ ), sputum IL-5 ( $p = 1.00$ ) or post-bronchodilator FEV<sub>1</sub> ( $p = 0.27$ ).

### Discussion

Our analyses show that treatment with prednisone or prednisolone is highly effective in reducing sputum eosinophils in eosinophilic bronchitis. This is accompanied by a reduction in other sputum inflammatory markers linked to eosinophilic bronchitis, such as ECP and IL-5. In addition, treatment of eosinophilic bronchitis with prednisone or prednisolone was shown to effect a significant increase in post-bronchodilator FEV<sub>1</sub>.

Data suggest that sputum eosinophilia and high levels of eosinophilic markers are associated with poor asthma control rather than with the severity

**Table 1** – Characteristics of the studies included.

Reference	Characteristics of the study	Treatment	Pre-treatment vs. post-treatment
Baigelman et al. <sup>(30)</sup>	Design: observational  Sample: 11 asthma patients (3 males and 8 females; 29-60 years of age) followed for at least 4 years  Profile: asthma exacerbation	Drug: prednisone  Dose: 80 mg/day  Duration: 3 days	Sputum eosinophils, mean $\pm$ SD: 26.0 $\pm$ 19.0% vs. 8.0 $\pm$ 5.0%  Sputum ECP: [not measured] post-bronchodilator FEV <sub>1</sub> , mean $\pm$ SD: 1.03 $\pm$ 0.41 L vs. 1.32 $\pm$ 0.51 L  IL-5: [not measured]
Claman et al. <sup>(31)</sup>	Design: randomized controlled trial  Sample: 24 asthma patients—oral prednisone group (n = 12, 7 males and 5 females) and placebo group (n = 12, 6 males and 6 females)—excluding patients having used inhaled or oral corticosteroids in the last 6 weeks, having had an upper respiratory infection in the last 6 weeks, and having a smoking history of > 10 pack-years  Profile: asthma exacerbation	Drug: oral prednisone  Dose: 0.5 mg/kg per day  Duration: 6 days	Sputum eosinophils, mean $\pm$ SE: 14.1 $\pm$ 5.0% vs. 1.8 $\pm$ 0.8%  Sputum ECP, mean $\pm$ SE: 325 $\pm$ 131 $\mu$ g/mL vs. 144 $\pm$ 84 $\mu$ g/mL  post-bronchodilator FEV <sub>1</sub> , mean $\pm$ SD: 88 $\pm$ 5.2% vs. 91 $\pm$ 4.87%  IL-5: [not measured]
Keatings et al. <sup>(34)</sup>	Design: single-blind crossover study  Sample: 15 COPD patients (excluded from this meta-analysis) and 11 patients with mild atopic asthma (1 excluded; 10 included for analysis; mean age 29.8 $\pm$ 3.4 years)  Profile: stable asthma	Drug: prednisolone  Dose: 30 mg/day Duration: 2 weeks	Sputum eosinophils, mean $\pm$ SD: 6.66 $\pm$ 0.98% vs. 0.99 $\pm$ 0.25%  Sputum ECP, mean $\pm$ SD: 687.0 $\pm$ 87.0 $\mu$ g/L vs. 80.2 $\pm$ 14.2 $\mu$ g/L  post-bronchodilator FEV <sub>1</sub> :  -in %, mean $\pm$ SD: 95.9 $\pm$ 5.7% vs. [not described]  -in L, mean $\pm$ SE: [not described] vs. 3.92 $\pm$ 0.32 L  IL-5: [not measured]
Pizzichini et al. <sup>(8)</sup>	Design: observational  Sample: 10 asthma patients  Profile: asthma exacerbation	Drug: prednisone  Dose: 30 mg/day for 5 days, tapered to zero by day 10  Duration: 10 days	Sputum eosinophils, mean $\pm$ SD: 17.6 $\pm$ 10.0% vs. 0.89 $\pm$ 0.90%  Sputum ECP, mean $\pm$ SD: 5,338.4 $\pm$ 6690.7 $\mu$ g/L vs. 985.5 $\pm$ 1311.0 $\mu$ g/L  post-bronchodilator FEV <sub>1</sub> , mean $\pm$ SD: 1.5 $\pm$ 0.3 L vs. 2.5 $\pm$ 0.5 L  IL-5, mean $\pm$ SD: 201 $\pm$ 128 pg/mL vs. 0.0 $\pm$ 55.6 pg/mL
Pizzichini et al. <sup>(10)</sup>	Design: observational  Sample: 8 patients with prednisone-dependent asthma; >12% variability in FEV <sub>1</sub> , baseline mean, 18.5% (range, 13-27%)  Profile: severe asthma	Drug: prednisone  Dose: 30 mg/day  Duration: 7 days	Sputum eosinophils, mean $\pm$ SD: 16.3 $\pm$ 32.3% vs. 0.0 $\pm$ 0.5%  Sputum ECP, mean $\pm$ SD: 7480 $\pm$ 5240 $\mu$ g/L vs. 700 $\pm$ 784 $\mu$ g/L  post-bronchodilator FEV <sub>1</sub> , mean $\pm$ SD: 55.7 $\pm$ 6.84% vs. 80.0 $\pm$ 15.91%  IL-5, mean $\pm$ SD: 66.5 $\pm$ 150 pg/mL vs. 44.1 $\pm$ 86 pg/mL
Di Franco et al. <sup>(32)</sup>	Design: randomized controlled trial  Sample: 40 adult nonsmokers (9 males and 31 females; mean age, 45 $\pm$ 13 years; 3 excluded), in two arms—fluticasone (1,000 $\mu$ g/day; n = 18) and prednisone (n = 19)  Profile: asthma exacerbation	Drug: prednisone  Dose: 40 mg/day, tapered to 10 mg/day by reducing the dose by 5 mg every other day  Duration: 6 days	Sputum eosinophils: 52.0% [no SD or SE] vs. 11.0% [no SD or SE]  Sputum ECP: 904 $\mu$ g/L [no SD or SE] vs. [not described]  post-bronchodilator FEV <sub>1</sub> , mean $\pm$ SD: 51.5 $\pm$ 14.4% vs. 83.6 $\pm$ 21.1%  IL-5: [not measured]
Scheicher et al. <sup>(33)</sup>	Design: controlled observational  Sample: 51 subjects—21 normal subjects and 30 patients with asthma (13 males and 17 females; mean age, 41 years), 9 of whom were steroid-naïve—the 9 steroid-naïve patients receiving oral prednisone and being evaluated before and after the treatment  Profile: stable asthma	Drug: oral prednisone  Dose: 40 mg/day  Duration: 14 days	-
Dente et al. <sup>(29)</sup>	Design: randomized controlled trial  Sample: 59 patients with severe refractory asthma, randomized to receive prednisone (n = 39) or placebo (n = 20)  Profile: severe asthma	Drug: oral prednisone  Dose: 0.5 mg/kg per day  Duration: 2 weeks	-

ECP: eosinophil cationic protein.

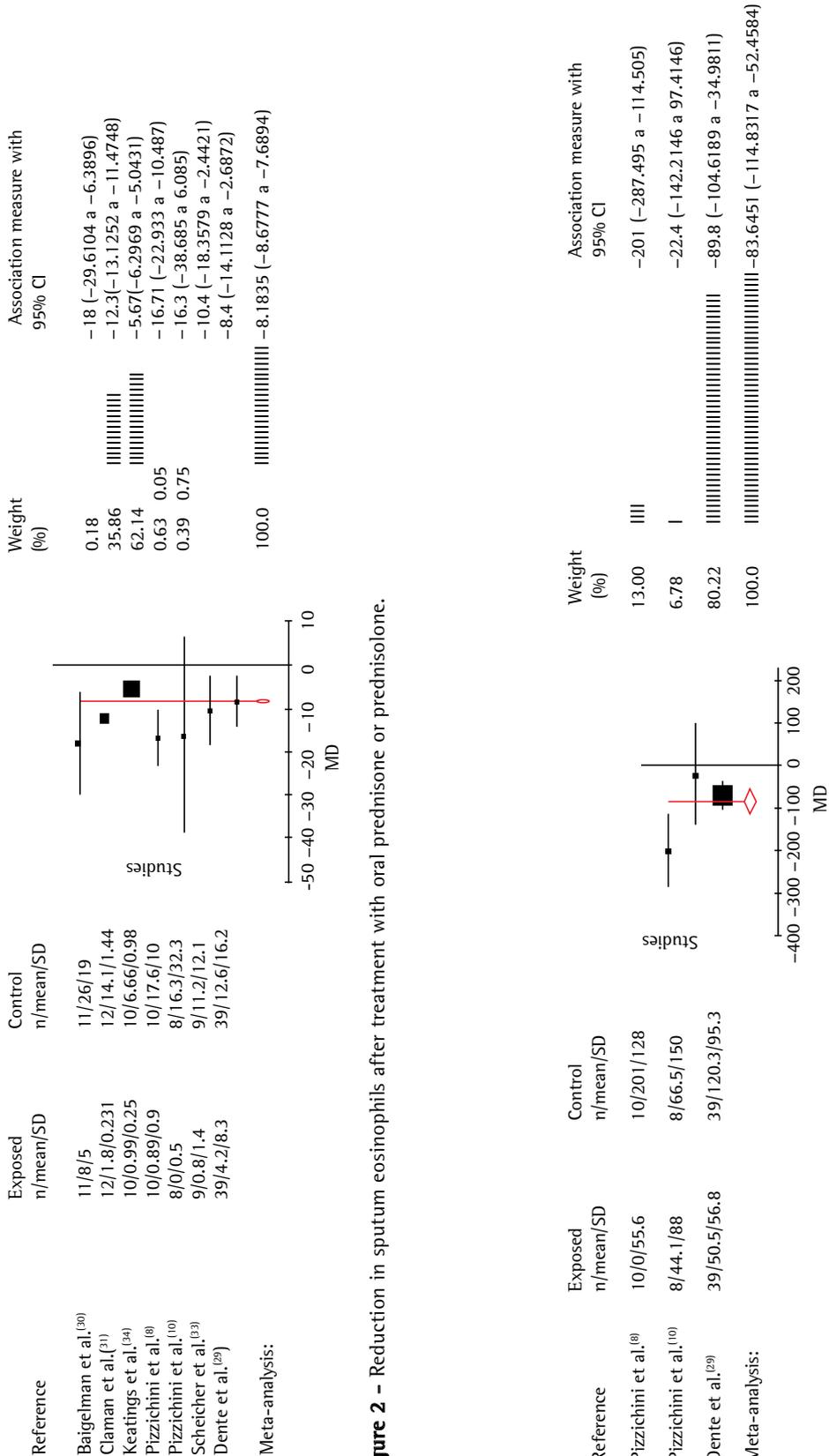
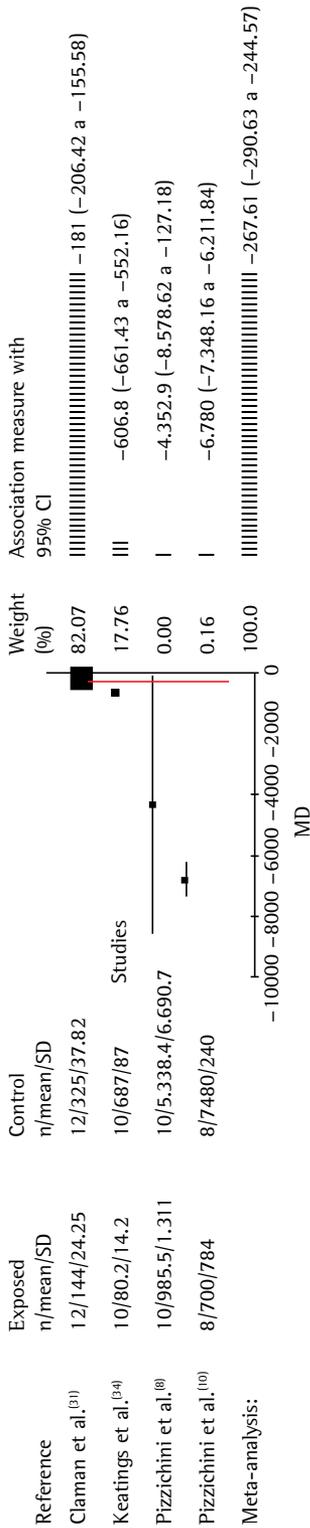
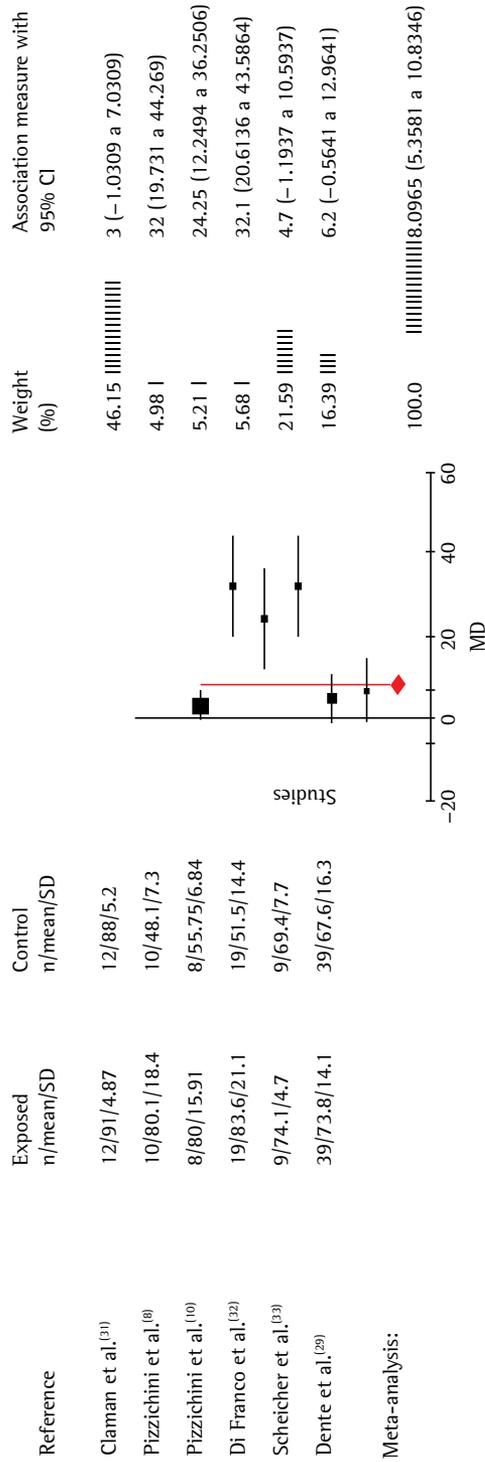


Figure 2 – Reduction in sputum eosinophils after treatment with oral prednisone or prednisolone.

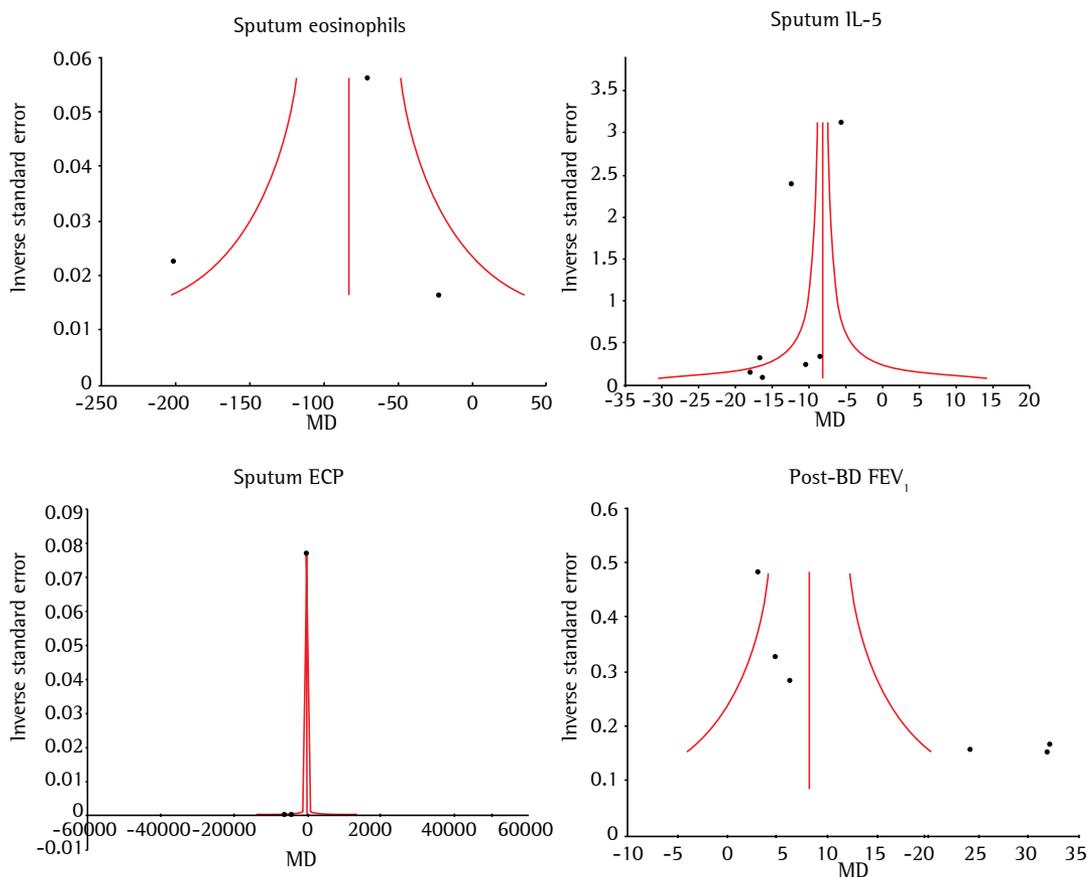
Figure 3 – Reduction in sputum IL-5 levels after treatment with prednisone.



**Figure 4** – Reduction in sputum levels of eosinophil cationic protein after treatment with oral prednisone or prednisolone.



**Figure 5** – Increase in post-bronchodilator FEV<sub>1</sub> (% of predicted) after treatment with prednisone.



**Figure 6** – Funnel plots. MD: median; ECP: eosinophil cationic protein; and BD: bronchodilator.

of asthma.<sup>(7,8,21,26)</sup> The corticosteroid-responsive component of asthma is eosinophilic bronchitis, which can now be recognized by the reliable method of counting cells in induced sputum samples.<sup>(6)</sup> Adequate treatment with corticosteroids reduces the proportion of eosinophils in sputum to within the normal range, even in prednisone-dependent asthma.<sup>(8,19)</sup> In this meta-analysis, there was a six-fold reduction in sputum eosinophils after treatment with prednisone or prednisolone.

Because a reduction in sputum eosinophilia is associated with a positive clinical and functional response to corticosteroids, our results support the recommendation to increase the dose of corticosteroids when asthma becomes uncontrolled.<sup>(8,21)</sup> In a multiple regression analysis, ten Brinke et al.<sup>(23)</sup> found that the most important factor potentially associated with persistent airflow limitation in severe asthma was a proportion of eosinophils in sputum > 2% (adjusted OR = 7.7). However, there are individuals with

uncontrolled asthma who do not present with sputum eosinophilia. Whether that subgroup could be less responsive to corticosteroids remains to be established.

Eosinophils have long been regarded as key inflammatory mediators in the pathogenesis of asthma, although their exact role is unclear. In studies of heterogeneous populations of subjects with asthma, the downregulation of eosinophil activity via targeted inhibition of IL-5 (a pro-eosinophilic cytokine) has yielded disappointing results.<sup>(35)</sup>

In one study of patients with severe asthma and refractory eosinophilic airway inflammation,<sup>(22)</sup> intramuscular administration of triamcinolone was found to reduce the mean proportion of eosinophils in sputum from 12.6% to 0.2%, similar to the reductions achieved through the use of inhaled corticosteroids (> 1,600 µg/day) or chronic oral prednisone.<sup>(29,32)</sup> The authors also observed an increase in FEV<sub>1</sub> and a reduction

in the use of rescue medication.<sup>(22)</sup> These data are in agreement with those of other studies of asthma patients, confirming that sputum eosinophilia is a good predictor of the response to corticosteroids.<sup>(6-8,36)</sup> The reason for this distinct short-term effect of corticosteroids, as opposed to the well-known, positive, long-term effect of corticosteroids in most asthma patients, is not known.<sup>(29)</sup> One possible explanation is that non-eosinophilic inflammation might respond to corticosteroids more slowly than does eosinophilic inflammation.<sup>(37)</sup>

The data presented here support the usefulness of sputum eosinophil assessment in predicting when patients with severe asthma might benefit from an increase in the dose of corticosteroids.<sup>(6-8,29,36)</sup> Classifying severe asthma phenotypes as eosinophilic and non-eosinophilic might have clinical implications for the choice of pharmacological therapy.<sup>(7,19,29)</sup>

Persistence of eosinophilia in severe asthma could be a reflection of corticosteroid insensitivity, and refractory asthma might respond to the use of anti-IL-5 therapy with mepolizumab.<sup>(4,5,38,39)</sup> As previously mentioned, we found that sputum IL-5 levels decreased after treatment with prednisone or prednisolone. Because IL-5 is a pro-inflammatory cytokine that increases the recruitment, activation, and survival of eosinophils, it is considered of pivotal importance in the pathophysiology of asthma.<sup>(40)</sup> Ying et al.<sup>(41)</sup> showed that IL-5 is highly expressed in T cells, eosinophils, and mast cells in bronchial biopsy specimens collected from patients with asthma. Other studies have shown that sputum levels of IL-5 trend higher in patients with eosinophilic asthma, whereas those of IL-8 trend higher in patients with non-eosinophilic asthma.<sup>(29,42)</sup> There is evidence that IL-5 is detectable in the induced sputum of asthma patients and that sputum levels of IL-5 are higher in patients with severe asthma than in those with mild-to-moderate asthma.<sup>(10,42)</sup>

Our results show that systemic corticosteroids are effective not only in reducing sputum eosinophil counts but also in inhibiting the release of pro-inflammatory cytokines that play a relevant role in perpetuating airway inflammation in patients with refractory asthma. Our data agree with those of other studies showing that corticosteroids decrease the number of activated T

cells expressing messenger RNA of IL-4 and IL-5 in the BAL fluid of asthma patients, regardless of the severity of the asthma.<sup>(43)</sup> Our results also show that treatment with prednisone or prednisolone can effect a four-fold reduction in sputum ECP levels. When we considered the ECP levels in sputum supernatants, we found that those levels were associated with poor asthma control, further underscoring the fact that eosinophils play a role in this equation.<sup>(28)</sup> However, despite expectations that patients with severe asthma would show higher sputum ECP levels, Romagnoli et al.<sup>(21)</sup> observed no differences among groups of asthma patients, stratified by asthma severity, in terms of the sputum levels of ECP.

In a study of acute exacerbations of asthma, Baigelman et al.<sup>(30)</sup> demonstrated that FEV<sub>1</sub> improves within the first 24 h of treatment with prednisone or prednisolone, further improvement being observed after 48-72 h of such treatment. However, in a similar study, Belda et al.<sup>(44)</sup> found no change in FEV<sub>1</sub> in the first 24 h. Aggarwal & Bhoi<sup>(12)</sup> also studied acute exacerbations of asthma and suggested that intravenous methylprednisolone followed by oral methylprednisolone is a more efficacious and safer treatment regimen than is intravenous hydrocortisone followed by oral prednisolone. However, those authors employed clinical and spirometric evaluation alone, without analyzing inflammatory mediators in sputum or other respiratory secretions.

In a meta-analysis conducted in 1992, Rowe et al.<sup>(17)</sup> showed that the use of corticosteroids early in the treatment of asthma exacerbations reduces the number of hospital admissions in adults and children, as well as showing that corticosteroids are effective in preventing relapse in the outpatient treatment of asthma exacerbations. Oral and intravenous corticosteroids appear to have equivalent effects on pulmonary function in acute exacerbations,<sup>(17)</sup> and recent studies have shown that inhaled and oral corticosteroids are also equally effective.<sup>(24,32,33,44)</sup>

Despite the heterogeneity among the studies evaluated here, in terms of the doses and duration of treatment/follow-up,<sup>(8,10,29-31)</sup> most of the exposure to prednisone or prednisolone was at > 30 mg/day, which is sufficient to suppress sputum eosinophils, reduce ECP levels, and inhibit IL-5, as well as to increase FEV<sub>1</sub>. However, because of the high degree of heterogeneity, it was necessary

to perform a meta-regression to adjust for dose and duration of treatment.

Meta-analysis is a powerful tool for studying cumulative data from individual studies with small sample sizes and low statistical power. Pooling effects from individual studies through meta-analysis can increase the statistical power and can help detect modest differences in risk among study groups.

It is possible to achieve a detectable change in inflammatory indices during a 14-day course of treatment with corticosteroids. Clinical benefits and anti-inflammatory effects have been reported in asthma patients treated with such short regimens, which are commonly used in clinical practice.<sup>(12,34)</sup>

In conclusion, we found that, in patients with moderate-to-severe eosinophilic bronchitis, treatment with prednisone or prednisolone effected a significant reduction in sputum eosinophil counts, as well as in the sputum levels of IL-5 and ECP. This reduction in the inflammatory response was accompanied by a significant increase in post-bronchodilator FEV<sub>1</sub>.

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