
Effect of montelukast on bacterial sinusitis in allergic mice

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Background: In mice, allergic rhinitis augments the infectious and inflammatory response to *Streptococcus pneumoniae*-induced sinusitis.

Objective: To investigate the effects of cysteinyl leukotriene antagonism on the severity of bacterial infection.

Methods: We performed 3 parallel, placebo-controlled experiments. In the first, mice were ovalbumin sensitized and ovalbumin challenged to show the effects of montelukast on the allergic inflammation; in the second, we evaluated the effect of montelukast on *S pneumoniae* infection; in the third, we used mice that were both allergic and infected. Montelukast was given starting 2 days after sensitization until the day before euthanasia. One day after drug treatment began, the mice were inoculated intranasally with *S pneumoniae* in the infected groups. Nasal hypersensitivity was measured with histamine challenges before the first sensitization and on the day before euthanasia. On the fifth day after infection, mice were euthanized, nasal lavage was performed, bacteria were cultured, and inflammatory cells in the sinuses were quantified.

Results: Mice that were infected only tended toward having increased bacterial counts from nasal lavage in the montelukast-treated group. The mice that were allergic and infected experienced significantly higher bacterial counts ($P < .05$). All 3 montelukast treatment groups had significantly decreased eosinophil counts as well as T-lymphocyte counts.

Conclusions: Montelukast reduces the manifestations of allergic rhinitis in mice. Surprisingly, montelukast led to an increase in bacterial growth in infected mice. This suggests an effect of the cysteinyl leukotrienes on the innate response to bacterial infection.

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INTRODUCTION

Clinically, sinusitis is usually divided into acute, fulminant, recurrent acute, and chronic conditions based on the reported severity and duration of the illness.¹ Our study focused on acute bacterial rhinosinusitis. There are more than 10 million episodes of acute sinusitis in the United States each year, with *Streptococcus pneumoniae* being the most common causative organism.^{2,3} Despite this high prevalence, few definitive studies have been performed on the pathogenesis of this condition.⁴ The major limitation lies in the types of studies that can be done on human subjects. For a better understanding of the pathogenesis of sinusitis, we developed a mouse model of acute sinusitis that leads to self-limited, noninvasive disease, like its human counterpart.⁵

In any large group of patients with acute sinusitis, allergic inflammation appears to be one factor that plays an important role.⁶ Although there are no controlled evaluations comparing the prevalence of sinusitis in allergic and nonallergic populations, there is a strong clinical impression that suggests an association. Savolainen⁶ found the incidence of allergy to be 25% in a group of 224 patients with acute maxillary sinusitis,

which was significantly greater than the 16% incidence in a control group. Holzman et al⁷ reported an increased prevalence of allergic rhinitis in children with orbital complications of acute rhinosinusitis, and these complications occurred especially during pollinating seasons. In a study of 8,723 children, Chen and colleagues⁸ found the prevalence of sinusitis to be significantly higher in children with allergic rhinitis than in children without allergies.

Complementing these findings that allergic rhinitis occurs frequently in patients with sinusitis are data that show a high prevalence of sinus disease in patients with allergic rhinitis. Sinus radiographs are abnormal in more than 50% of adults and children who have perennial allergic rhinitis.⁹ Magnetic resonance imaging scans demonstrate increased evidence of sinus mucosal abnormalities during major pollinating seasons.¹⁰ In humans, acute sinus infections occur often during exposure to allergen and are a common reason for the failure of allergy treatment.¹¹ How allergic rhinitis affects the course of sinusitis is not clear.

Leukotrienes (LTs) are formed from arachidonic acid in response to multiple inflammatory stimuli. Phospholipase A₂ cleaves arachidonic acid from cell membrane phospholipids and turns the intermediate 5-hydroperoxyeicosatetraenoic into LTA₄ with the help of the enzyme 5-lipoxygenase. LTA₄ is modified intracellularly to form LTC₄, which is subsequently transported to the extracellular environment where additional enzymatic activation results in the formation of LTD₄ and then LTE₄. LTC₄, LTD₄, and LTE₄ are known as

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the cysteinyl leukotrienes (cysLTs). LTA₄ can also be converted to LTB₄. LTs are released from cell membranes of multiple cells, including eosinophils, mast cells, basophils, and neutrophils.¹²

The effects of cysLTs are mediated through 2 receptors, CysLT₁ and CysLT₂. Neutrophils express only CysLT₁, but mast cells and eosinophils express both receptors.¹³ The roles of cysLTs in the pathogenesis of allergic rhinitis are well established, with randomized controlled trials confirming the efficacy of LT receptor antagonists when they are used as monotherapy.¹⁴ Elevated production of cysLTs is characteristic in the nasal mucosa of patients with chronic rhinosinusitis, particularly in the subset of patients with chronic hyperplastic eosinophilic sinusitis.¹⁵ Their role in the pathogenesis of acute bacterial rhinosinusitis has yet to be determined. The effects of cysLT antagonists have not been demonstrated in the scenario of allergic rhinitis with a concurrent bacterial sinusitis, the aim of our study. We hypothesized that the cysLT antagonist montelukast would decrease the augmentation of bacterial sinusitis in mice during an ongoing allergic reaction.

METHODS

Mice

BALB/c mice of either sex, aged 6 to 8 weeks, were obtained from Jackson Laboratory (Bar Harbor, ME) and kept in microisolation cages in the Carlson Biocontainment Suite at The University of Chicago. These animals received an ovalbumin-free diet. The Institutional Animal Care and Use Committee of The University of Chicago approved the protocol.

Study Design

We performed 3 experiments. In the first experiment, uninfected, allergic mice were treated with either montelukast or placebo (group A). In the second experiment, infected, non-allergic mice were treated with either montelukast or placebo (group B). In the third experiment, infected, allergic mice were treated with either montelukast or placebo (group C). Each of the 3 groups included mice that were noninfected, not allergic, and not treated with montelukast or placebo to serve as controls for flow cytometry. Mice were sensitized, challenged, inoculated, gavaged, and euthanized as shown in Figure 1.

The number of mice in each group was determined by a power calculation. Based on prior data, we calculated the number of mice per group by using 90% power to detect a difference among groups of animals euthanized on day 5 for the primary outcome variable, the number of bacteria recovered from lavages, by using a 2-tailed significance level of .05. We needed 8 mice per group.

Allergen Sensitization

The allergic groups (groups A and C) were sensitized with ovalbumin as follows: a 100-μg/mL ovalbumin solution in alum was prepared by dilution of ovalbumin (Sigma Chem-

ical Co, St Louis, MO) with phosphate-buffered saline (PBS) and alum inject adjuvant (Pierce, Rockford, IL). Two hundred microliters of this solution was injected intraperitoneally into each mouse.

Allergen Exposure

The allergic groups (groups A and C) were challenged daily with droplets of intranasal solutions that consisted of 50 μL of 6% ovalbumin solution in PBS. The nonallergic group of mice (group B) was challenged with 50 μL of PBS.

Inoculation

The infected groups (groups B and C) were inoculated intranasally with *S pneumoniae* (ATCC49619) for induction of acute bacterial rhinosinusitis as described previously.⁹ The *S pneumoniae* was grown on sheep blood agar plates, and colonies were suspended in sterile saline solution at McFarland No. 3 concentration (approximately 1.2×10^9 CFU/mL). A suspension of 25 μL of *S pneumoniae* was placed dropwise into each nostril. As obligate nose breathers, mice inhaled the solutions into their nasal passages.

Medication

A suspension of 25 mg/kg daily of montelukast in 0.1M PBS was fed via gavage tube to half of the mice in each group (groups A, B, and C). The remaining mice were gavaged with 0.1M PBS as placebo treatment. The dose, which is high compared with the dose of montelukast in humans, results from the high metabolic rate of rodents compared with humans and was based on published data on the use of montelukast in mice.¹⁶

Nasal Challenges

Nasal symptoms were evaluated for each mouse in each group by counting of the number of sneezes that occurred in the 5-minute interval after nasal challenge with 6% ovalbumin or PBS. The individual counting the sneezes was blinded to all aspects of the protocol. Fifty microliters of 0.3-, 3.0-, and 30-mmol/L solutions of histamine were used to challenge the mice at 10-minute intervals. The same individual counted sneezes and rubs for 5 minutes after each histamine challenge. The cumulative response to all doses of histamine was calculated by addition of the responses at the 3 challenge doses and was used for statistical analysis.

Tissue Harvesting and Processing

Flow cytometry was used for quantifying cells present in the sinuses. The mice were euthanized, and the skull was bisected sagittally for exposure of the sinuses. The tissue from the sinuses was removed and processed as previously described.¹⁷ The surface expression of various markers was evaluated with Summit software on a Cyan flow cytometer. Surface expression was determined by use of the following fluorescence isothiocyanate (FITC)- and phycoerythrin (PE)-conjugated antibodies: GR1-FITC, CD11b-PE, CD3-FITC, CD4-PE, CCR3, and CD8-FITC.

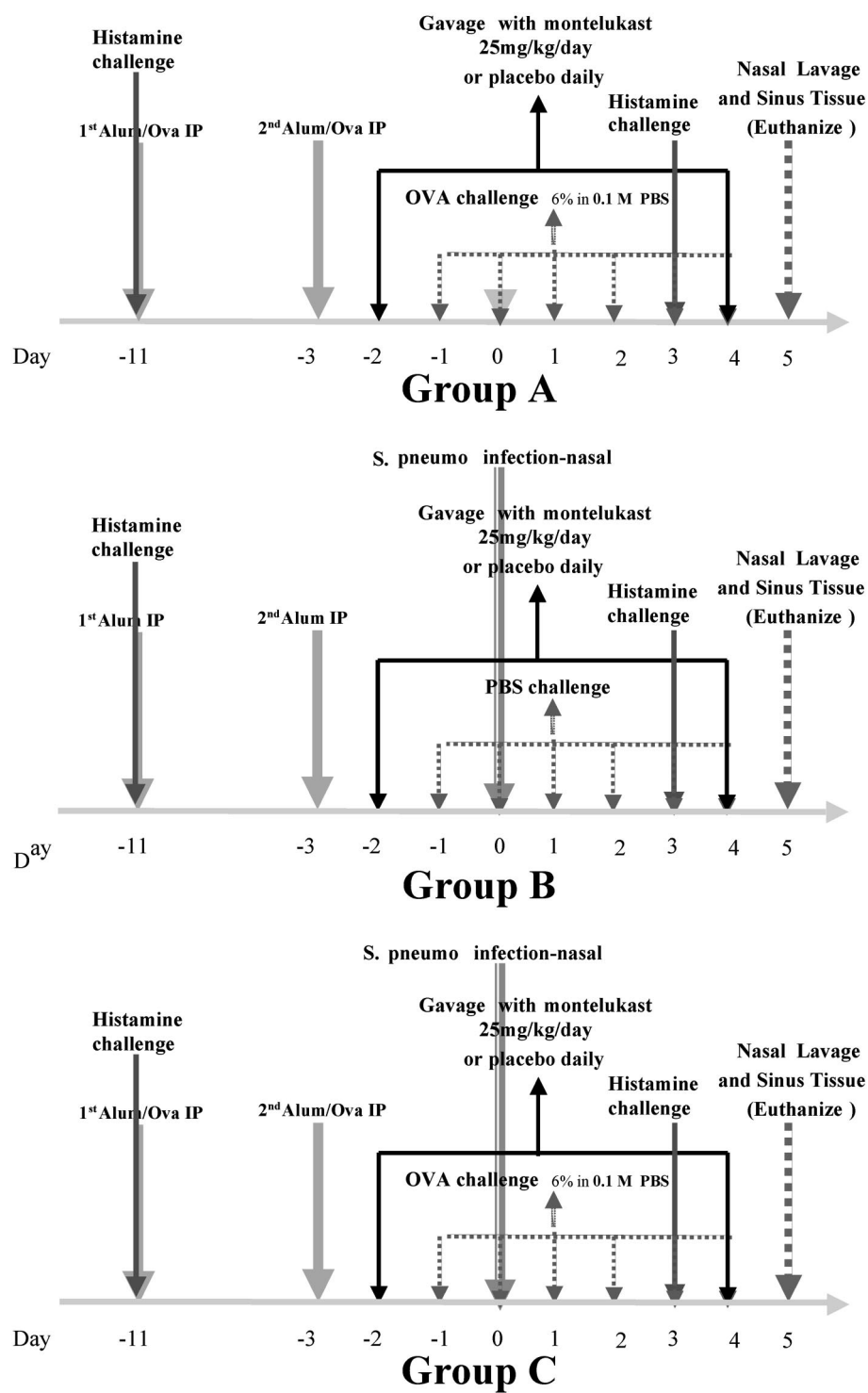


Figure 1. Study design detailing the experimental protocols for the 3 experimental groups. IP indicates intraperitoneally; S. pneumo, *Streptococcus pneumoniae*; PBS, phosphate-buffered saline; OVA, ovalbumin.

Nasal Cultures

On the day of euthanasia, mice were sedated with a respiratory-failure dose of 120 mg/kg of pentobarbital sodium (Nembutal) given by intraperitoneal injection, and nasal lavage was performed with 200 μ L of PBS. The lavage liquid was then serially diluted (neat, 1:10, 1:100, 1:1000, and 1:10,000), and each dilution was plated onto Columbia sheep blood agar plates. The plates were incubated for 24 hours, and then the number of colonies was counted.

Our technique to quantify bacteria is a standard microbiologic approach performed routinely in the Microbiological Laboratories at The University of Chicago Hospitals. Quantification of the infecting organism is a standard approach to monitoring an infection in experimental animal models and in certain clinical situations in humans. Our techniques are reproducible and responsive to change, and we believe that this is clearly demonstrated in our prior publications.^{17,18} The number of bacteria in lavages was shown to have an excellent correlation with quantitative cultures taken simultaneously from the sinuses.¹⁹ Note that we mimic the clinical disease of acute sinusitis, which is closer to colonization than infection. Neither our model nor the human disease is marked by systemic signs of infection like fever, which can be quantified.

Statistical Analysis

Log conversion for normalization was performed on the flow cytometry and culture data. Differences were first compared by 1-way analysis of variance. If they were significant, the Tukey multiple comparison test was used for post hoc analysis. $P < .05$ was considered to indicate statistical significance.

RESULTS

We first tested the efficacy of montelukast in treating allergic rhinitis in mice by analyzing the results for the allergic-only group (group A). The mice were sensitized and then treated with montelukast or placebo daily. Twenty-four hours after montelukast treatment, the mice were exposed to intranasal ovalbumin. On day 5, treatment with montelukast significantly reduced the number of CD3⁺, CD11b⁺, CCR3⁺, and GR1⁺ cells compared with placebo treatment and increased the number of CD8⁺ cells (Table 1). The response to nasal challenge with histamine after ovalbumin exposure was increased significantly in both groups. The amount of sneezing

on day 3 tended to be less after montelukast treatment than after placebo ($P = .13$) (Fig 2). In aggregate, these data suggest that montelukast at the given dose was effective in inhibiting the allergic reaction with respect to cellular infiltration.

Next, we asked whether montelukast affected the response to a gram-positive bacterial infection by examining the results for the infected only group (group B). On day 5, the number of colonies of *S pneumoniae* recovered tended to be higher in the montelukast-treated ($P = .08$) than that in the placebo-treated group (Fig 3). There was increased sneezing on the third day after infection in response to histamine compared with that before inoculation of the *S pneumoniae* in both the montelukast and placebo groups, with no difference between the groups (Fig 4). There were fewer CCR3⁺ and GR1⁺ cells in the sinuses of the group treated with montelukast compared with the placebo-treated group (Table 1).

In the third experiment (group C), we addressed the effect of montelukast on the augmented infectious and inflammatory response in infected, allergic mice. The group treated with montelukast had significantly more bacteria recovered on day 5 compared with the placebo group ($P = .01$) (Fig 5). Increased sneezing in response to the histamine challenge occurred in the placebo-treated group. Montelukast significantly blocked this increase in hyperresponsiveness ($P = .04$) (Fig 6). Montelukast reduced the number of CD3⁺, CD4⁺, CD8⁺, CCR3⁺, GR1⁺, and CD11b⁺ cells relative to placebo treatment.

DISCUSSION

Montelukast had the expected positive effect on allergic rhinitis in mice. Similar to its efficacy in human subjects with allergic rhinitis, montelukast decreased the number of inflammatory cells during the allergic response and also resulted in a tendency to reduce the allergen-induced reactivity to histamine. In contrast, montelukast treatment tended to lead to more bacterial colonization by *S pneumoniae*, which became more significant in allergic and infected mice than in infected-only mice. What is the mechanism for this observation and what is the potential relevance of this finding to humans?

LTs are produced by all myeloid cell lineages in response to a wide range of stimuli. They have been shown to be generated during allergic reactions in humans and mice and are best known as bronchoconstrictors and vasoactive medi-

Table 1. Cellular Response in Sinus Tissues Assessed by Flow Cytometry

	Allergic only			<i>P</i> value	Infected only			<i>P</i> value	Allergic and infected			<i>P</i> value
	Placebo	Montelukast			Placebo	Montelukast			Placebo	Montelukast		
CD3 ⁺ , $\times 10^6$ cells/mL	8.1 $\pm$ 0.5	5.8 $\pm$ 0.4		.03	6.2 $\pm$ 0.7	4.6 $\pm$ 0.7		.20	6.6 $\pm$ 1	4.3 $\pm$ 0.5		.007
CD4 ⁺ , $\times 10^6$ cells/mL	1.5 $\pm$ 0.2	1.8 $\pm$ 0.4		.16	2.4 $\pm$ 0.3	1.3 $\pm$ 0.4		.11	1.9 $\pm$ 0.1	1.2 $\pm$ 0.2		.003
CD8 ⁺ , $\times 10^6$ cells/mL	1.4 $\pm$ 0.2	1.9 $\pm$ 0.4		.02	1.0 $\pm$ 0.1	1.0 $\pm$ 0.1		.69	1.3 $\pm$ 0.2	1.2 $\pm$ 0.2		.03
CD11b, $\times 10^7$ cells/mL	1.7 $\pm$ 0.2	1.8 $\pm$ 0.4		.08	4.0 $\pm$ 0.6	2.7 $\pm$ 0.5		.12	3.2 $\pm$ 0.4	3.1 $\pm$ 0.7		.05
CCR3 ⁺ , $\times 10^7$ cells/mL	3.6 $\pm$ 0.2	2.2 $\pm$ 0.2		.004	1.0 $\pm$ 0.1	0.07 $\pm$ 0.03		<.001	5.3 $\pm$ 0.4	2.4 $\pm$ 0.2		<.001
GR1, $\times 10^7$ cells/mL	1.1 $\pm$ 0.2	1.5 $\pm$ 0.4		.008	2.6 $\pm$ 0.2	1.4 $\pm$ 0.2		.01	7.4 $\pm$ 0.3	1.8 $\pm$ 0.4		<.001

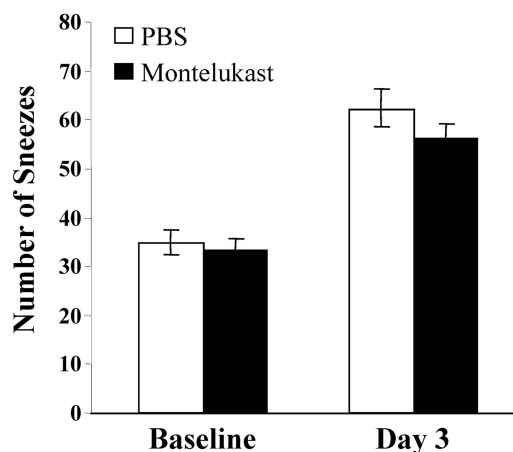


Figure 2. Histamine responsiveness in allergic mice. The y-axis depicts the number of sneezes in response to histamine challenge at baseline and at day 3 of the experiment, 4 days after initiation of the ovalbumin challenge. PBS indicates phosphate-buffered saline.

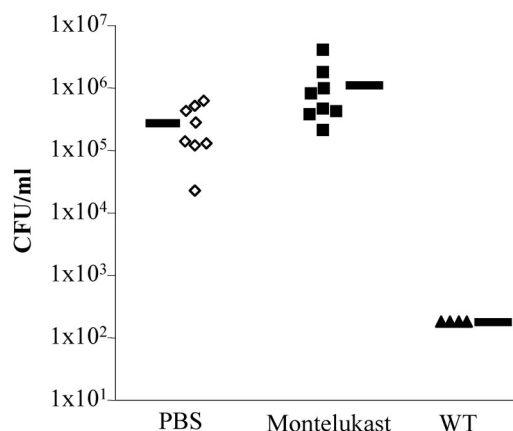


Figure 3. *Streptococcus pneumoniae* in nasal lavages 5 days after inoculation into the sinuses of nonallergic mice. The x-axis marks the 3 groups: mice receiving placebo treatment (phosphate-buffered saline [PBS]), mice receiving montelukast, and wild-type (WT) control mice. Solid bars represent medians.

ators released by allergen-triggered mast cells that contribute to asthmatic and allergic responses.²⁰ Although the effects on the vasculature are probably of limited importance in our model, the effect on the innate immune system could explain our findings. The role of LTs in innate immune responses is not as well understood but is increasingly being recognized, because they can be generated in response to microbial stimuli and they mediate a variety of antimicrobial functions. Thus, an antagonistic effect of these functions by montelukast might explain our observations of an increased response to *S pneumoniae* in the actively treated infected and allergic mice compared with the placebo-treated ones.

Activation of LT synthesis has been recognized in response to bacteria, fungi, viruses, and protozoa in patients and ani-

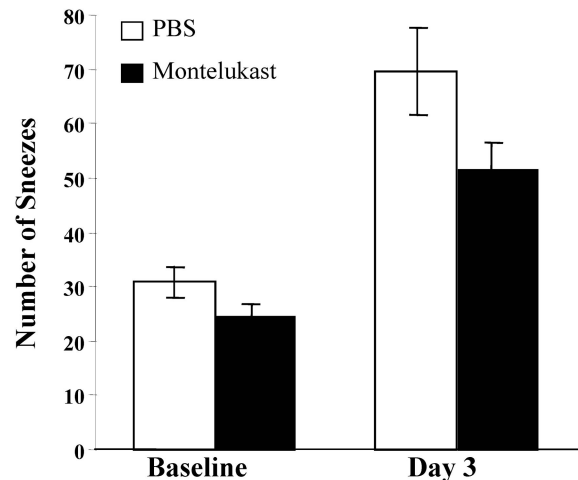


Figure 4. Histamine responses of infected mice. The y-axis depicts the number of sneezes in response to histamine challenge in the infected mice at baseline and 3 days after *Streptococcus pneumoniae* inoculation. There were no significant differences between the groups. PBS indicates phosphate-buffered saline.

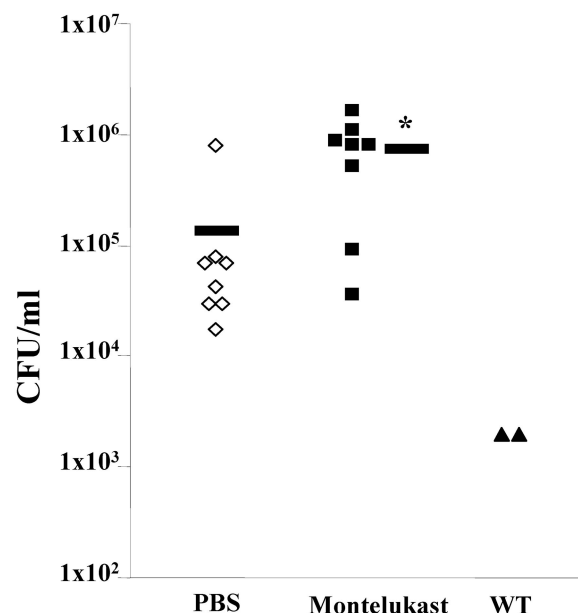


Figure 5. *Streptococcus pneumoniae* in nasal lavages 5 days after inoculation into the sinuses of allergic mice. The x-axis marks the 3 groups: mice receiving placebo treatment (phosphate-buffered saline [PBS]), mice receiving montelukast, and wild-type (WT) control mice. Solid bars represent medians. **P* = .01.

mal models and in vitro in isolated leukocytes.²¹ In rabbit models of lung injury, *Escherichia coli* stimulates release of LTC₄.²¹ Furthermore, LT knockout mice have a higher mortality when challenged with *Klebsiella pneumoniae* than do wild-type mice, suggesting that these molecules impart an antimicrobial effect.²¹ Microbial activation of LT biosynthe-

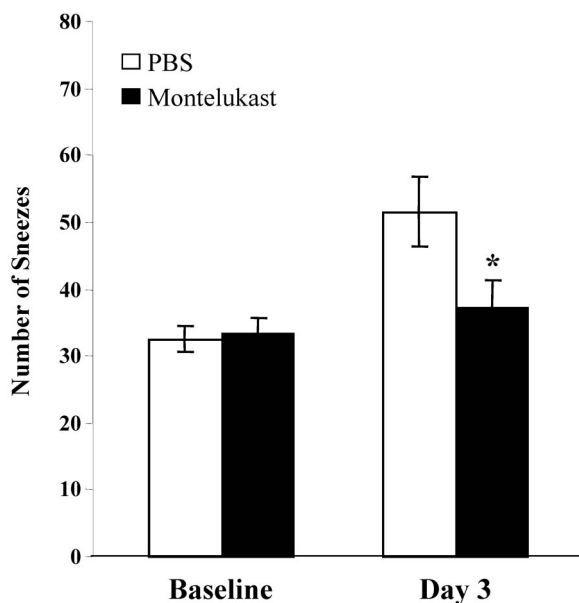


Figure 6. Histamine responses of infected allergic mice. The y-axis depicts the number of sneezes in response to histamine challenge in the infected or allergic mice at baseline and 3 days after *Streptococcus pneumoniae* inoculation. * $P = .04$ vs phosphate-buffered saline (PBS).

sis has been shown to occur not only in phagocytes but also in eosinophils²² and mast cells, which release small amounts of LTB_4 and LTC_4 in response to bacterial challenge in vitro.¹³ This observation has added potential importance to our model of allergic and infected mice, in which the augmentation of *S pneumoniae* by montelukast treatment was most pronounced as the number of eosinophils and mast cells increased during the allergic reaction.

LTs impart antimicrobial effects by a variety of mechanisms. They are important mediators of leukocyte accumulation during acute inflammation.¹² CysLTs augment microvascular permeability and thereby facilitate movement of leukocytes from the circulatory system to sites of inflammation.¹³ Furthermore, they contribute to leukocyte accumulation in tissues by enhancing their survival via inhibition of apoptosis of neutrophils²³ and eosinophils.²⁴ CysLTs generated by macrophages participate in dendritic cell trafficking to sites of antigen stimulation²⁵ and to lymph nodes.²⁶ LTC_4 enhances macrophage phagocytosis and also promotes innate immune responses indirectly through the elaboration of other inflammatory mediators, such as cytokines and chemokines, which themselves activate leukocyte recruitment and antimicrobial activity. Examples of such mediators include cysLT-induced production of interleukin 5, tumor necrosis factor α , and macrophage inflammatory protein 1 β by mast cells.²¹ In addition to their effects on leukocyte accumulation and phagocytosis, LTs impart antimicrobial activity by the augmentation of killing of several microorganisms, including bacteria.²¹ CysLTs induce nitric oxide (an important mediator

of antimicrobial defense) generation in human neutrophils,^{27,28}

The clinical significance of our findings is unknown. One might speculate that increased bacterial colonization in allergic individuals would lead to more infections. In support of this concept, many disease states associated with a relative LT deficiency, such as diabetes mellitus, cigarette smoking, and vitamin D deficiency, are associated with increased susceptibility to infection.²¹ The *Physicians' Desk Reference* describes an increased incidence of respiratory tract infections in children, but this has not translated into significant infectious problems in the large numbers of children with asthma and allergic rhinitis who are treated with montelukast. Asthma, an atopic disease like allergic rhinitis, was found to be a risk factor for invasive pneumococcal disease. Although oral steroids were not found to direct the association, there was no mention of the role of LT modifiers.²⁹ On the other hand, montelukast has been given to millions of patients with asthma and allergic rhinitis, and there has been no reported increase in bacterial infections. However, because most upper respiratory tract bacterial infections are low grade and more than 60% of acute episodes of bacterial rhinosinusitis will respond to placebo treatment, it may be difficult to detect an increased prevalence of infections without a careful search. Furthermore, the reduction in inflammation associated with montelukast might reduce patients' symptoms. Montelukast produces a relative, not an absolute, deficiency of cysLTs. The reintroduction of 5-lipoxygenase inhibitors might lead to an increased incidence of infections because of effects on both the cysLTs and LTB_4 , the latter of which is of potential importance in leukocyte accumulation and phagocytosis.^{12,27,28}

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