Role of Type 1 T Helper Cells in the Resolution of Acute *Streptococcus pneumoniae* Sinusitis: A Mouse Model

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**Background.** We examined the importance of the adaptive and innate immune responses in the resolution of an acute bacterial sinus infection in mice.

**Methods.** Recombinase-activating gene knockout (RAG-1/−/−) (no lymphocytes) and C57BL/6 (wild-type) mice were infected with *Streptococcus pneumoniae*. For determination of the cell type involved, lymphocytes from mice were adoptively transferred into RAG-1/−/−, C57BL/6 (all lymphocytes), B cell–deficient, and T cell–deficient mice. The degree of infection and inflammation was determined by quantification of *S. pneumoniae* from nasal lavage and analysis of sinus tissue, respectively.

**Results.** In C57BL/6 mice, both the infection and inflammation resolved in 21 days, whereas neither resolved in RAG-1/−/− mice. When C57BL/6 lymphocytes were adoptively transferred into RAG-1/−/− mice, resolution of the infection and inflammation occurred. Mice without B cells were able to clear the infection, whereas mice without T cells could not clear it. In vitro stimulation of the draining lymph nodes of the infected mice by use of heat-killed *S. pneumoniae* led to the production of interferon (IFN)–γ. Flow-cytometric analysis of lymphocytes obtained from sinus mucosa and draining lymph nodes showed an increase in the number of type 1 T helper cell–like cells over that in control mice.

**Conclusions.** RAG-1/−/− mice with innate immunity but no lymphocytes contain—but cannot clear—a bacterial sinus infection. Lymphocytes transferred to RAG-1/−/− mice clear the infection. The sinus mucosa and draining lymph nodes show an increase in T cells generating IFN-γ. These data demonstrate that T cells are essential in clearing an acute *S. pneumoniae* bacterial sinus infection.

Sinusitis is usually divided into acute, fulminant, recurrent acute, and chronic conditions, on the basis of the reported severity and duration of the illness in patients [1]. The present study focuses on acute bacterial sinusitis.

Acute sinusitis is estimated to follow 1% of viral upper respiratory tract infections [2]. Gwaltney thus estimated that there are ~10 million episodes of acute sinusitis in the United States each year [2]. These episodes are usually treated with antibiotics. The increase in antibiotic usage is a major reason for the increase in bacterial resistance to antibiotics [3]. In 1996, $5.8 billion was spent on the care of patients with sinusitis [4]. Thus, each year, billions of dollars are spent on direct medical costs for treatment of this enigmatic illness.

Despite the high prevalence of sinusitis, there have been limited studies of the etiology of, pathogenesis of, and therapy for this condition. *Streptococcus pneumoniae* is the organism most frequently cultured from the maxillary sinuses of patients who have acute sinusitis [5, 6]. Treatment of acute sinusitis with antibiotics is superior to placebo treatment, although the infection will resolve in 60% of placebo-treated patients [7, 8], suggesting that antibiotics do not explain the entire issue. The limited morbidity associated with the typical case of acute sinusitis implies that this is not an infection marked by tissue destruction and high mortality but is an illness that impedes quality of life. We pre-
viously developed a mouse model of acute sinusitis that mimics these observations [9–11].

New insights into the mechanism of acute bacterial sinusitis should lead to novel strategies for decreasing the duration of the illness, its morbidity, the development of resistant organisms, and its economic burden. To date, investigations have focused primarily on the bacteria and on the development of vaccines and antibiotics. Instead, in the present study, we turned our focus on gaining a better understanding of the host’s immune response to the bacteria that cause acute sinusitis. We hypothesized that the innate immune system contains the infection and that the acquired immune system then eliminates it. We further hypothesized that Th1 cells contribute to eliminating the bacterial infection.

MATERIALS AND METHODS

Experimental animals. Pathogen-free 6–8-week-old C57BL/6J, C57BL/6.129S7-RAG−/− (recombinase-activating gene knockout [RAG-1−/−]), B6.129P2-Tcrβ−/− (T cell–deficient), B6.129S2-Igh−/− (B cell–deficient), and BALB/c mice were purchased from Jackson Laboratories. These animals were kept in microisolator cages in a pathogen-free biohazard containment facility. All animals were used in protocols approved by the Animal Care and Use Committee of the University of Chicago.

Infection. S. pneumoniae (ATCC 49619) was used for induction of acute sinusitis. The strain is antigenically similar to type 19 S. pneumoniae, the most common strain cultured from human sinuses [12, 13]. Fifty microliters of an S. pneumoniae suspension (1.2 × 10^7 CFU/mL) was placed in the nares of each mouse.

Nasal cultures. The mice were sedated, and a nasal lavage was performed with 200 μL of PBS. The recovered lavage fluid was then serially diluted (undiluted and diluted 1:10, 1:100, 1:1000, and 1:10,000), and 10 μL of each dilution was plated onto Columbia sheep’s blood agar plates. The plates were incubated for 48 h, and then colonies of S. pneumoniae were counted. The results were quantified as the number of colony-forming units per milliliter. We previously showed that lavage cultures correlate (r = 0.848; P < 10^-6) with cultures of ground sinus tissue [11].

Tissue harvesting and processing. For histologic analysis, the mice were sedated with a respiratory-failure dose of pentobarbital sodium at 120 mg/kg. The sinuses were then processed as described elsewhere [9]. Sections of the nasal passages and sinuses were cut at a thickness of 8 μm, mounted on glass slides, and stained with hematoxylin-eosin.

Flow-cytometric analysis was used for quantifying the cells present in the sinuses and lymph nodes. To perform the technique, the mice were killed. We removed the skin and tissue from the head and then sagittally bisected the skull, exposing the sinuses. The tissue from the sinuses was removed manually. The harvested tissue was placed in 2 mL of PBS. We added 2 mL of PBS with collagenase P (Roche Diagnostics) at a concentration of 2 mg/mL. The tissue was incubated at 37°C for 1 h in a water-bath shaker. After tissue degradation, the suspension was then passed through a Nyctex filter (Sefar-America), and the cells were recovered in Dulbecco’s MEM with 5% fetal calf serum (FCS) (medium). Next, we centrifuged the cells for 5 min at 4°C and 375 newtons and discarded the supernatant (these were the centrifuge conditions throughout all experiments). We then suspended the cell pellet in 2 mL of 5% medium and quantified the cells by use of 0.4% trypan blue on a hemocytometer. Using the calculated live cell number, we next prepared samples of aliquoted cells at concentrations between 5 × 10^3 and 1 × 10^5 cells/fluorescence-activated cell sorting (FACS) tube. All of the tubes were filled with FACS buffer and centrifuged for washing of the cells. We then added 20 μL of 2.4 G2 (an anti-Fc receptor used to stop nonspecific binding) and incubated the tubes for 15 min at room temperature. Ten microliters of the antibody or antibodies diluted to the previously determined titration amount was added and incubated for 45 min at 4°C. After incubation, we again added FACS buffer and centrifuged. Finally, we added 300 μL of FACS buffer. Flow cytometry was performed on a 3-detector BD FACScan or a 6-detector BD LSR (Becton Dickinson). The markers we examined were GR1 (neutrophils), CD11b (macrophages), CD3, CD4, CD8, and CD19 or B220 (B cells).

Adoptive transfer. To modify the immune systems of the mice, we used the technique of adoptive transfer. We used cells harvested from homogeneic donor animals. The lymph nodes and spleens were harvested and processed into a single-cell suspension by either gentle grinding between sterile frosted slides (lymph nodes) or gentle pressing with a 3-mL syringe plunger. The processing was performed in medium without FCS. The cells were then Nyctex-filtered and centrifuged. The red blood cells were removed by addition of 2 mL of ACK lysis buffer (Biosource International) to the cell pellet for 1 min. The cells were then washed with 15 mL of 5% medium, centrifuged, and resuspended in 1 mL of 0.1 mol/L PBS. The cell concentration was then calculated, and the cells were diluted so that 100 μL contained the desired number of cells for transfer. Once the cells were properly suspended, they were immediately injected into the recipient animals via the orbital vein by use of a 30-gauge needle.

In vitro lymphocyte-cytokine stimulation. The draining lymph nodes were harvested and homogenized by use of sterile glass slides for grinding the tissue. The cells were then washed with medium, centrifuged, and resuspended. Next, we counted the live cells on a hemocytometer by use of 0.4% trypan blue. The spleens were also harvested and prepared as described in the Adoptive Transfer subsection above. After lysing of red blood cells.
cells and washing of the remaining cells, the splenocytes were irradiated for 15 min at 3000 rad. We prepared heat-killed bacteria by taking inoculum at $1 \times 10^7$ organisms and incubating it in a 45°C water bath for 45 min. We tested the success of this method by streaking plates with the heat-killed inoculum and found no colony growth. Gram stains of the heat-killed S. pneumoniae showed intact bacteria. When all cells had been prepared, they were added together on 96-well plates. One-hundred-microliter aliquots of medium, containing $1 \times 10^8$ cells of each cell population, were added to a well, giving a total volume of 200 μL. Finally, 10 μL of sterile saline containing $1 \times 10^8$ heat-inactivated S. pneumoniae was added, and the 96-well plates were incubated for 72 h at 37°C.

**Statistical analysis.** Log conversion was performed on the culture data before analysis. Parametric 2-tailed t tests were used for data analysis when values exceeded the limits of detection. When values were below the limits of detection, nonparametric tests were performed. $P<.05$ was considered to indicate significance.

**RESULTS**

**Development of acute sinusitis.** Mice (C57BL/6) were anesthetized, an inoculum of S. pneumoniae was introduced into the nose, and then the mice were allowed to recover. After 1 h, 6 $\times 10^8$ organisms, on average, were recovered by lavage. This recovery is remarkable, considering that mucociliary clearance would be expected to reduce nonbinding, nonproliferating organisms by 90% in 1 h, an observation that we reproduced by measuring the recovery of heat-killed S. pneumoniae. Over the next several days, the recovery of organisms remained fairly constant before they were cleared (figure 1).

Because of concerns about the size of the initial inoculum, we performed studies in which we dosed with S. pneumoniae over 4-log concentrations, beginning with $1 \times 10^8$ organisms and going to $1 \times 10^6$ organisms. Cultures from mice were analyzed 5 days after inoculation. Despite a decrease in the initial inoculum, the number of organisms recovered on day 5 was similar in all groups, suggesting that the microenvironment reached a plateau for bacterial growth.

We also homogenized the lungs of 17 mice used for comparison of nasal lavage culture and quantified the number of S. pneumoniae organisms. All of the lungs grew S. pneumoniae, but the levels were ∼100-fold lower than those in the sinuses. This finding is compatible with published results indicating that nasal inoculation leads to pneumonia [14]. Nevertheless, the reason for our mice not becoming ill and dying was probably related to the serotype of the organisms we selected.

**RAG-1−/− mice and sinusitis.** We first tested our hypothesis that T cells are involved in the response to bacterial infection by use of RAG-1−/− mice to demonstrate the relative roles of the innate and acquired immune systems. RAG-1−/− mice have complete loss of all lymphocytes, disruption of the gene that leads to T cell receptor (TCR)–β expression, and loss of αβ T cells [15]. We looked at the response on days 7, 14, and 21 after inoculation. The RAG-1−/− mice had the same initial response to infection on day 7 as did their wild-type C57BL/6 counterparts. They had comparably high levels of polymorphonuclear cell (PMN) infiltrates within the sinuses, PMN clusters within the sinus cavities, and S. pneumoniae recovered from lavage. On day 14 after inoculation, we began to see fewer cells in the infiltrates and fewer clusters in the C57BL/6 mice, a difference that reached significance by day 21. Twenty-one days after inoculation with S. pneumoniae, C57BL/6 mice were able to resolve their infection and inflammation, whereas RAG-1−/− mice still contained large numbers of bacteria and significantly higher levels of PMNs within their sinuses. These data suggest that the innate immune system contains S. pneumoniae infection; however, lymphocytes are required for the resolution of the infection and inflammation (figure 2).

**Acute sinusitis in RAG-1−/− mice into which C57BL/6 lymphocytes were adoptively transferred.** We next used the technique of adoptive transfer to support the role of T cells. To ensure that the lymphocytes were populating the RAG-1−/− mice, we adoptively transferred $15 \times 10^7$ or $75 \times 10^6$ C57BL/6 cells into the RAG-1−/− mice. Five days after the adoptive transfer, we analyzed the RAG-1−/− lymph nodes by flow cytometry, to look for extracellular T cell marker (CD3) and B cell marker (B220). Lymphocytes repopulated the lymph nodes.

We next proceeded to evaluate the immune response to S. pneumoniae infection in RAG-1−/− mice into which C57BL/6 lymphocytes were adoptively transferred. We chose 21 days after inoculation as the end point, because we saw the greatest differences between RAG-1−/− and wild-type C57BL/6 mice on that day. We adoptively transferred cells harvested from the

![Figure 1](https://academic.oup.com/jid/article-abstract/192/7/1237/2191870)
spleen and lymph nodes of C57BL/6 mice, at 2 doses, into RAG-1−/− mice and compared the response to those in RAG-1−/− and C57BL/6 mice (figure 3). As before, the RAG-1−/− mice contained the infection but were unable to resolve the infection and inflammation as well as did mice with the wild-type phenotype. The transfer of C57BL/6 lymphocytes enabled RAG-1−/− mice to resolve the infection (figure 3) and inflammation (figure 4), making their reaction to S. pneumoniae similar to that of C57BL/6 mice.

**Acute sinusitis in RAG-1−/− mice with adoptively transferred lymphocytes lacking either T or B cells.** We next asked whether it was the B or T cells that were responsible for the resolution of the infection by day 21. We transferred lymphocytes from B cell– or T cell–deficient mice. The infection in the C57BL/6 mice resolved, but the infection in the RAG-1−/− mice did not, and the adoptive transfer of all lymphocytes restored the ability of RAG-1−/− mice to clear the infection. RAG-1−/− mice into which lymphocytes from T cell–deficient mice had been transferred were unable to clear the infection. In contrast, RAG-1−/− mice into which lymphocytes from B cell–deficient mice had been transferred were able to clear the infection, suggesting the importance of T cells in resolving acute bacterial sinusitis (figure 5).

**IFN-γ and IL-4 production in vitro.** To determine which subpopulation of T cells was responding to the S. pneumoniae, we quantified the cytokine production from the draining lymph nodes in vitro. We infected C57BL/6 mice with S. pneumoniae. Five days after inoculation, we harvested and stimulated the lymphocytes with heat-killed S. pneumoniae for 3 days. IFN-γ production was elevated in mice with sinusitis, compared with that in the uninfected negative control mice. At the same time, both groups had undetectable amounts of IL-4.

Histologic analysis was effective for evaluating neutrophils and eosinophils, but analysis of T cells and other cells was difficult. Therefore, we applied flow-cytometric analysis to harvest sinus mucosa. An example of the analysis of an infected mouse and an uninfected mouse is shown in figure 6. The infected mouse had more GR1 and CD4 staining than did the control mouse.

**IFN-γ and IL-4 T cell staining in draining lymph nodes and sinus mucosa.** We next used intracellular techniques to identify the subsets of Th cells in the draining lymph nodes and sinus mucosa of infected mice. Because of the small number of T cells, we infected 5 mice and harvested their draining lymph nodes and sinuses 5 days after inoculation. We compared

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Figure 2. Infection of recombinase-activating gene knockout (RAG-1−/−) mice. RAG-1−/− and wild-type control mice were inoculated with Strep-tooccus pneumoniae and killed at various days after inoculation. Each symbol represents 1 mouse. Diamonds represent C57BL/6 mice, circles represent RAG-1−/− mice, and triangles represent uninfected wild-type mice. The dashed line represents the level of detection. Values below the level of detection are plotted as half the value of the level of detection. *P < .01, RAG-1−/− mice vs. C57BL/6 mice on day 21.

Figure 3. Adoptive transfer: sinus cultures. We inoculated recombinase-activating gene knockout (RAG-1−/−) mice (RAG), RAG-1−/− mice into which we adoptively transferred 15 × 10⁶ or 75 × 10⁶ lymph node (LN) cells, and C57BL/6 mice (B6) with Streptococcus pneumoniae and cultured the sinuses 21 days later. Each symbol represents 1 mouse. The dashed line represents the level of detection. Values below the level of detection are plotted as half the value of the level of detection.
the disease in humans. RAG-1 knockout mice develop a model of acute sinusitis that closely mimics "-itis" is added to the site where the inflammation occurs, such localized infection. In essence, if host defenses are effective, Acute sinusitis, like other diseases of the airway, is a self-limited, DISCUSSION

ed mice. This observation suggests that a Th1-like response is separately. Both groups showed evidence of CD4+ and CD8+ IFN+ cells (figure 7). There were greater percentages of CD4+ and CD8+ IFN+ cells in the infected mice than in the uninfected mice. This observation suggests that a Th1-like response is important in the inflammatory response to infection.

Acute sinusitis, like other diseases of the airway, is a self-limited, localized infection. In essence, if host defenses are effective, "-itis" is added to the site where the inflammation occurs, such as sinusitis, otitis, and pneumonitis [16]. In our studies, we have developed a model of acute sinusitis that closely mimics the disease in humans. 

S. pneumoniae has >90 serotypes, which vary enormously in their potential to cause disease [12]. The serotypes recovered from infected sinuses in humans are not the ones used for inducing pneumonia in mice [17]. In fact, mice inoculated intranasally with type 3 pneumococcus routinely die within 48 h. We carefully chose the strain of S. pneumoniae, rather than the types of strains typically associated with meningitis or fatal pneumonia, to mimic acute sinusitis in humans. The strain used in our studies has a serotype similar to the strains routinely recovered from patients with acute sinusitis [12]. We have shown a similar response to the strain used in the present study and 2 strains of S. pneumoniae obtained from patients with acute sinusitis (authors’ unpublished data).

In most studies in humans, treatment of acute sinusitis with antibiotics is superior to placebo treatment, in that it causes faster resolution of the illness [7, 8]; we have duplicated these findings in our model [10]. Invasive complications of infectious sinusitis, such as orbital abscesses, are extremely rare after episodes of acute sinusitis [18]. This last observation points to the limited morbidity associated with the typical case of acute sinusitis. For a better understanding of the pathogenesis of sinusitis, we developed a mouse model of acute sinusitis that leads to self-limited, noninvasive disease, as is seen in its human counterpart [7, 19], in which the pathogenesis can be investigated.

We have shown that normal, immunocompetent C57BL/6 mice have an acute infectious and inflammatory response to S. pneumoniae that peaks at approximately day 7 and resolves by day 21. When RAG-1−/− mice, which have the same genetic background as do C57BL/6 mice but lack B cells and T cells, are infected, they, too, develop acute sinusitis. In these animals, the innate response is able to contain the bacteria so that the animals do not become septic. However, an immune response lacking lymphocytes is unable to resolve the infection and the associated inflammation within the sinus. RAG-1−/− mice into which C57BL/6 lymphocytes were adoptively transferred resolved sinusitis in a way similar to C57BL/6 mice, supporting the importance of lymphocytes in the resolution of sinusitis. Furthermore, RAG-1−/− mice into which T cells were adoptively transferred were able to resolve the bacterial infection, unlike RAG-1−/− mice given B cells.

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Figure 4. Adoptive transfer: polymorphonuclear cell (PMN) infiltrates. We inoculated recombinase-activating gene knockout (RAG-1−/−) mice (RAG), RAG-1−/− mice into which we adoptively transferred 15 × 10^5 or 75 × 10^5 lymph node (LN) cells, and C57BL/6 mice (B6) with Streptococcus pneumoniae and examined PMN infiltrates in the sinus mucosa 21 days later. Each symbol represents 1 mouse. *P < .05.

Figure 5. Adoptive transfer. We inoculated recombinase-activating gene knockout (RAG-1−/−) mice (RAG), RAG-1−/− mice into which we adoptively transferred 75 × 10^5 lymphocytes from B cell–deficient mice (RAG + B cell Def), RAG-1−/− mice into which we adoptively transferred 75 × 10^5 lymphocytes from T cell–deficient mice (RAG + T cell Def), RAG-1−/− mice into which we adoptively transferred 75 × 10^5 lymphocytes from C57BL/6 mice (RAG + B6), and C57BL/6 mice (B6) with Streptococcus pneumoniae and quantified the number of colony-forming units of S. pneumoniae recovered 21 days later. Each symbol represents 1 mouse. The dashed line represents the level of detection. Values below the level of detection are plotted as half the value of the level of detection. *P < .01.
Figure 6. Flow-cytometric analysis of granulocytes and CD4+ cells in sinus mucosa harvested on day 5 after inoculation with Streptococcus pneumoniae (infected) or broth (uninfected). There were increased numbers of GR1+ cells (upper panels) and CD4+ cells (lower panels) in the infected mouse, compared with the uninfected mouse. FITC, fluorescein isothiocyanate; PE, phycoerythrin.

To determine the subpopulation of T cells responding to the S. pneumoniae infection, we used heat-killed S. pneumoniae to stimulate T cells from the draining lymph nodes of infected C57BL/6 mice. This specific stimulation caused a Th1 cytokine profile. Additionally, we were able to harvest T cells from the draining lymph nodes and sinuses of infected mice, and we showed that an increased percentage of the lymphocytes produced IFN-γ. These studies support the concept that Th1 cells are needed for resolving acute bacterial sinusitis caused by extracellular bacteria.

One might criticize our model by suggesting that we are studying colonization rather than infection. If one defines “infection” as multiplication of microorganisms followed by invasion of body tissue and subsequent growth, production of toxins, and injury to that tissue, then acute sinusitis in humans is not an infection, because it is rarely associated with tissue invasion or destruction. Acute sinusitis, however, is associated with the recovery of pathogenic organisms from secretions in titers >1 × 10⁴ and an inflammatory response, in contrast to these parameters in appropriate controls [5].

Colonization is not associated with tissue destruction [20]. Prolonged colonization is considered harmful, and vaccines have been developed to prevent it. Thus, “colonization” may be a better term than “infection” when acute sinusitis in humans is described. Our model mimics sinusitis in humans by recovering organisms in high titers and showing an inflammatory response in the sinus tissue. Although our model may not mimic infection according to the classic definition, it mimics acute sinusitis in humans.

The response to S. pneumoniae infection has been shown to involve several pathways [21]. Complement activation by the alternative pathway is used initially to contain infections and is believed to play a role in the local neutrophil response [22]. Pneumolysin, the principal cytotoxin of S. pneumoniae, inhibits ciliary beating and can both activate the classical complement pathway and subvert the complement response [23]. An antibody response to infection occurs [24]. The role of T cells in the sinus response to S. pneumoniae has not been a major focus of in-
vestigation [25]. Numbers of antigen-specific CD8+ cells, which secrete microbiocidal molecules, expand and contract in ~1 week, which correlates with clearance of a pathogen in an acute infection [26, 27]. Our studies showed a small increase in the number of CD8+ cells. In mouse models of *S. pneumoniae* infection, in which death at 48 h is an end point, T and B cells accumulate within this time frame [28]. Furthermore, the increase in pneumococcal disease in patients with AIDS is related to an absolute CD4+ cell count <200 cells/mm³, supporting the role of T cells in the control of streptococcal infections [29, 30].

The innate immune system is the result of steady-state resistance caused by physical barriers and the consequence of activation of multiple cellular and soluble factors that lead to the release of acute reactants, which promote phagocytosis and stimulate further cytokine and chemokine production [31–33]. In the present study, the RAG-1−/− mice with intact innate immune systems were able to contain the infection but could not eliminate it. The ability to eliminate the infection was restored by the transfer of T cells.

A factor that is equal in importance to the way the host defends against infection is how the host resolves the inflammation after the organism is eliminated. There are numerous diseases, such as tuberculosis, in which ongoing inflammation persists after the initial insult caused by the infecting organism. Carding and Egan suggested that γδ T cells terminate the host response to infection by interacting with macrophages [33]. Apoptosis and subsequent phagocytosis by macrophages are the usual mechanisms for clearing inflammatory cells [34]. Extracellular bacteria can induce T cell apoptosis by use of toxins [35]. Interestingly, avirulent strains of *S. pneumoniae*, like the strain that we used, induce more apoptosis than do other strains [36]. Investigators have suggested that controlling inflammation prevents the sequelae of *S. pneumoniae* infection [37–39].

Understanding how immunocompetent mice resolve infection could lead to novel therapies that bring about a more rapid resolution of both the infection and secondary inflammation, thus improving patients’ quality of life and reducing the duration of antibiotic treatment and, thus, the growing problem of bacterial antibiotic resistance. In contrast, factors that prolong inflammation may be important in the development of chronic sinusitis. In conclusion, we have shown in the present study that Th1 cells are associated with the resolution of acute bacterial sinusitis in mice.

References


