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Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis

To the Editor:

The role of bacterial colonization or infection in chronic rhinosinusitis (CRS) is unclear and has not been thoroughly investigated in CRS with nasal polyps (NPs), a subgroup of patients with often severe eosinophilic inflammation, a high recurrence rate, and frequent asthma comorbidity and aspirin sensitivity.¹ In the whole group of patients with CRS, a *Staphylococcus aureus* carriage rate of 35% was observed at the middle meatus.² *S aureus* also frequently colonizes the nostrils in healthy subjects and may form enterotoxins, which under appropriate conditions can penetrate the mucosal barrier and possibly act as superantigens on T and B lymphocytes. This can induce a polyclonal stimulation with consecutive eosinophilic inflammation and IgE formation. We have recently shown that in approximately 50% of nasal tissue homogenates derived from NPs, IgE antibodies specific to classical staphylococcal enterotoxins (*Staphylococcus aureus*-derived enterotoxins [SAEs] A and/or B) could be found. This was linked to high concentrations of total IgE and a local polyclonal IgE antibody formation against various inhalant allergens.³ Furthermore, in polyp samples with SAE-specific IgE antibodies, a severe eosinophilic in-

flammation was present, demonstrated by the upregulation of IL-5, eotaxin, eosinophil-cationic protein (ECP), and cysteinyl-leukotriene synthesis. In addition, most of these patients had asthma and aspirin hypersensitivity.³ The presence of IgE antibodies to SAEs A, C, and toxic shock syndrome toxin 1 (SAE mix) has also been studied in healthy controls, in subjects with mild asthma, and in patients with severe asthma, defined by the need for regular high-dose inhaled corticosteroid therapy and, despite this treatment, persistently impaired lung function.⁴ In these groups, IgE antibodies to SAE mix were found significantly more often in serum from patients with asthma compared with controls, especially when comparing patients with severe asthma with controls (62% vs 13%; $P = .01$). This suggests a relationship between the presence of IgE antibodies to SAEs in serum and the severity of asthma.

In this study, we aimed to investigate the rate of colonization of the middle nasal meatus by *S aureus* in controls ($n = 9$, 4 males, 5 females; mean age, 38.4 years), subjects with CRS ($n = 22$, 11 males, 11 females; mean age, 49 years) and subjects with NP ($n = 55$, 36 males, 19 females; mean age, 48 years), as well as subgroups of the latter characterized by comorbid asthma ($n = 18$) and aspirin sensitivity ($n = 8$). Only 1 of the patients with asthma had current atopic dermatitis but was not colonized. None of the other patients had previous or current atopic dermatitis in their medical history.

The tissue was homogenized with a mechanical homogenizer (B. Braun, Melsungen, Germany) at 1000 rpm for 5 minutes on ice. After homogenization, the suspensions were centrifuged at 3000 rpm for 10 minutes at 4°C, after which the supernatants were separated and stored at -80°C until analysis. Blood samples were clotted at room temperature for 20 minutes and centrifuged at 1500 for 10 minutes at 4°C, and the serum was separated. ECP and total IgE and specific IgE against *Staphylococcus* enterotoxin A, *Staphylococcus* enterotoxin C, and toxic shock syndrome toxin 1 (SAE mix) levels were measured in tissue and serum using the Uni-CAP system (Pharmacia & Upjohn, Uppsala, Sweden).⁵ Immunocap coated with human serum albumin or glycine was used to evaluate any nonspecific binding of IgE.

Colonization rates in controls and subjects with CRS were 33.3% and 27.3%, whereas 63.6% ($P < .05$ vs CRS) of all subjects with NP were colonized with *S aureus*, with rates of 66.7% and 87.5% in the NP subgroups with asthma and aspirin sensitivity ($P < .05$ vs CRS for both), respectively (Fig 1, A). Repeated swabbing of the middle meatus in 8 subjects with NP suggested long-term colonization with *S aureus*. However, the factors that determine carrier and noncarrier status are largely unknown, and this question awaits further prospective studies.

The prevalence of IgE antibodies to SAEs in tissue homogenates paralleled colonization rates (Fig 1, B) but was always lower. Probably not only colonization with *S aureus* but also another event, which could be a viral infection, is necessary to induce this specific immune

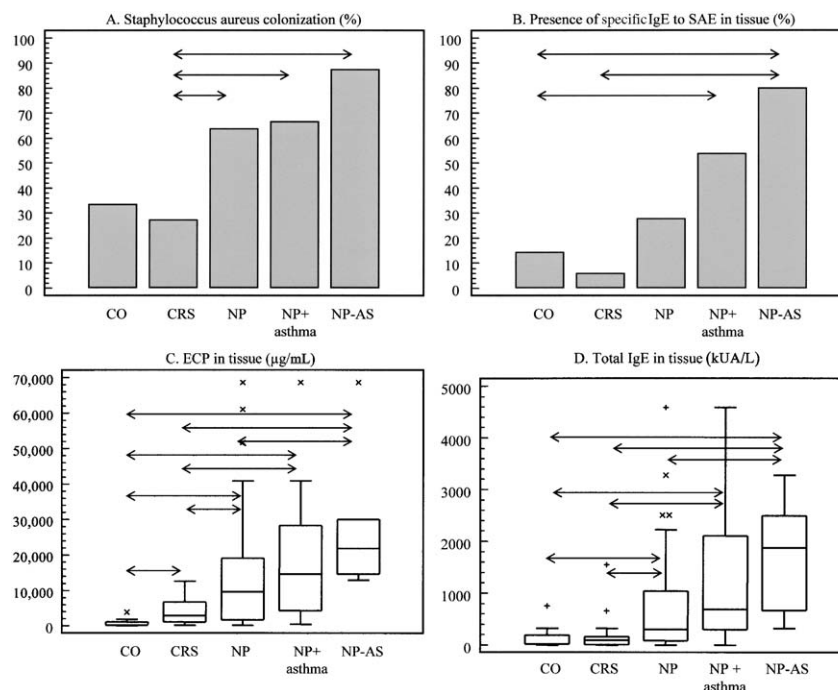


FIG 1. **A**, Isolation rate of *S aureus* from the middle meatus in controls (CO) and subjects with CRS, NPs, NPs with asthma (NP-asthma), and NPs with aspirin sensitivity (NP-AS), expressed as percentage (number of positive cases/total number). **B**, Demonstration of IgE antibodies to SAE mix in nasal tissue homogenates of the same patients expressed as percentage (number of positive cases/total number). Statistical analysis: χ^2 test with Yates correction (arrow, $P < .05$). **C**, ECP concentrations, and **D**, total IgE antibody concentrations in nasal tissue homogenates of the same patients. The box plot represents the median, the lower to the upper quartile, and the minimum to the maximum value, excluding outside and far out values (displayed as separate points). Statistical analysis: Mann-Whitney U test (arrow, $P < .05$).

response. This relation was especially noted in the NP group, in which 63.6% of subjects were colonized but only 27.8% demonstrated an IgE response. In contrast, 66.7% of subjects with NP and asthma were colonized, but as many as 53.8% formed IgE to SAEs. We therefore hypothesize that the superantigen activity of SAEs locally in the nasal and sinus cavities may have a systemic impact on the lower airways, possibly by release of inflammatory mediators into the circulation. Furthermore, the chance of finding specific IgE to SAEs in mucosal tissue in patients with NPs with concomitant asthma was 7 times higher (odds ratio, 7.78; 95% CI, 1.52-39.75) compared with patients without asthma. In the same patient groups (controls, CRS, NP), specific IgE to the SAE mix was measured in serum. In controls, 14.3% of the patients had specific IgE to *S aureus* enterotoxins in their serum. Specific IgE was also present in the serum of CRS and NP in 7.1% and 22.6%, respectively. Only 1 patient with NP with concomitant asthma and 1 patient with aspirin intolerance had specific IgE in the serum. Statistical analysis revealed no significant differences between all groups. These findings reflect the local production of IgE and specific IgE in the polyp tissue.

The levels of ECP and total IgE in tissue from aspirin-sensitive patients with NP were significantly higher compared with NP, CRS, and control groups. The same

finding was seen for NP with asthma compared with the other groups (Figs 1, C and D). As described,³ ECP and total IgE production were significantly upregulated in NPs compared with controls and CRS. Furthermore, the concentrations of ECP and total IgE antibodies were significantly increased in NP samples with the presence of IgE antibodies to SAEs versus samples without (NP with specific IgE vs NP without specific IgE for ECP, $P = .005$; for IgE, $P < .0001$). These findings suggest the strong proinflammatory and IgE-inducing effects of *S aureus* enterotoxins in nasal tissue.

To summarize, this is the first report on increased colonization of nasal polyps with *S aureus*, combined with a local immune response that consists of an IgE formation and eosinophilic inflammation in the majority of samples. Interestingly, this phenomenon can rarely be found in CRS without polyps, separating the 2 disease entities. In subjects with NPs and comorbid asthma or aspirin sensitivity, rates of colonization and IgE response in nasal tissue homogenates were further increased, paralleled by increases of ECP and total IgE. Finally, the presence of a local immune response to superantigens, characterized by IgE formation to SAEs, is strongly associated with asthma in patients with NP.

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Treatment of infants coinfectd with HIV-1 and cytomegalovirus with combination antiretrovirals and ganciclovir

To the Editor:

Infants coinfectd with HIV-1 and cytomegalovirus (CMV) experience rapidly progressive disease, leading to immunologic deterioration and poor survival.¹ As for adults, treatment of infants with highly active antiretroviral therapy (HAART) has been successful, leading to a significant decrease in mortality and delayed disease progression. In association with a decrease in plasma HIV-1 RNA, there is a restoration of CD4⁺ lymphocytes, which could lead to better immune control for various viral infections, including CMV and HIV-1.

Ganciclovir has been reported to be effective for the treatment of CMV-induced diseases in the immunocompromised host. However, little information is available regarding the efficacy of ganciclovir for congenital CMV infection. Phase II-III studies of ganciclovir for symptomatic congenital CMV have shown a decreased incidence of hearing loss in infants treated with ganciclovir, suggesting that preemptive therapy might prevent the recurrence of disease and neurologic damage in infants infected with CMV.^{2,3} We hypothesized that the addition of ganciclovir therapy to HAART early in life in infants coinfectd with

HIV-1 and CMV could lead to better preservation of viral-specific immunity and thus improve overall survival and disease outcome related to both viruses.

Three infants were given diagnoses of CMV and HIV-1 infections between 1 and 6 months of age. The dose of ganciclovir used in these patients was 5 mg/kg per dose every 12 hours intravenously for 2 weeks as induction therapy, followed by either 5 mg/kg per dose every 24 hours intravenously or 30 mg/kg/day every 8 hours orally as maintenance therapy. HAART was also initiated after the identification of HIV infection. Sustained plasma HIV-1 RNA of less than 400 copies/mL and normal CD4⁺ lymphocyte counts and percentages were achieved in each of the 3 study patients.

Patient 1 (Fig 1, A). A 6-month-old girl was hospitalized with a 2-month-history of persistent cough and cyanosis. Her weight, height, and head circumference were less than the fifth percentile for age. Chest roentgenography showed diffuse bilateral pulmonary infiltrates. The diagnosis of CMV-induced pneumonitis was made by means of positive viral culture from the lung tissue obtained by open lung biopsy. Head computed tomography showed intracranial calcifications consistent with congenital CMV infection. Her initial plasma HIV-1 RNA was 931,000 copies/mL, and her CD4⁺ lymphocyte count was 550/μL (20%) (normal range, 1800-4000/μL [35% to 56%]).⁴ Brainstem auditory evoked responses showed bilateral sensorineural hearing loss. Six weeks after discontinuation of ganciclovir treatment, her plasma CMV DNA PCR result became positive, and an additional 8-week course of ganciclovir was instituted. Since that time, she has achieved sustained suppression of both CMV and HIV-1. Although she has made developmental progress, she remains developmentally and physically delayed at 3 years of age.

Patient 2 (Fig 1, B). A 3-month-old girl was given a diagnosis of CMV-induced hepatitis and HIV-1 infection. On physical examination, her weight, height, and head circumference were less than the fifth percentile. Generalized lymphadenopathy and hepatosplenomegaly were noted. The aspartate aminotransferase level was 390 U/L, and the alanine aminotransferase level was 347 U/L. Her plasma HIV-1 RNA was 518,000 copies/mL, and her CD4⁺ lymphocyte count was 2337/μL (41%) (normal range, 1600-4000/μL [35% to 64%]).⁴ After the initiation of HAART and ganciclovir therapy, the plasma CMV DNA PCR result became negative, and the patient's plasma HIV-1 RNA levels became less than 400 copies/mL. Results of a hearing test were normal at 12 months of age. A head magnetic resonance imaging scan showed increased signal in the bilateral periventricular white matter consistent with congenital CMV infection. She has shown continued developmental progress but has required speech therapy for her language delay.

Patient 3 (Fig 1, C). A 2-month-old girl was hospitalized with the diagnosis of HIV-1 infection and CMV-induced hepatitis. The aspartate aminotransferase level was 116 U/L, and the alanine aminotransferase level was 347 U/L. A urine viral culture result was positive for CMV