

# Reducing Fungal Exposure Critical for Treating Rhinosinusitis with or without Polyps [Response to Letter]

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## Dear editor

We thank Dr Curtis for his interest in our article,<sup>1</sup> and welcome the opportunity to address the putative role of molds and fungi in chronic rhinosinusitis (CRS).

The potential contribution of fungi to the pathophysiology of CRS has been a focus of investigation many years back, and showed strong variation depending on the environment and climate.<sup>2,3</sup> The emerging understanding that the nose and sinuses naturally host a microbiome including viruses, bacteria, and fungi, suggests that the presence of microorganisms is itself not a key etiological factor in CRS.<sup>4</sup> Moreover, there is a lack of convincing immunological data to link fungi to the disease process in the great majority of CRS cases.<sup>5</sup> Consistent with this understanding, a 2018 Cochrane Review found no good evidence that oral or topical antifungals have a positive effect of quality of life, symptoms, or signs of disease in patients with CRS.<sup>6</sup> Indeed, consensus guidelines advise against the use of antifungals in CRS.<sup>4</sup>

Among the phenotypes of CRS, allergic fungal rhinosinusitis (AFRS) is recognized as distinct from CRS with nasal polyps (CRSwNP), which was the subject of our review, in its diagnosis, presentation, clinical course, pathophysiology, and management.<sup>4,7,8</sup> AFRS is a chronic disease that occurs predominantly in warm, humid climates and is characterized by a robust type 2 inflammatory response directed against colonizing fungi with accumulation of eosinophilic mucin containing fungal hyphae leading to persistent sinus opacification and nasal polyp formation. However, there is good evidence that AFRS accounts for only approximately 5–10% of CRS cases.<sup>4,9–12</sup> The study referenced in Dr Curtis' letter, which reported presence of AFRS in 94 of 101 CRS surgical patients, investigated a heterogeneous population of patients with CRSwNP as well as CRS without nasal polyps diagnosed by recurrent upper tract infections lasting longer than 3 months and inflammatory mucosal thickening,<sup>13</sup> which is not consistent with the current diagnostic criteria for CRSwNP,<sup>4</sup> and reported a large heterogeneity in polyp size from "minimal" to "massive". The contribution of fungi to CRS in this study is particularly unclear since 100% of the control population were reported as culture-positive for fungi, with a microbiome profile similar to that of CRS patients.

While the potential association between CRS, including AFRS, and exposure to mold is an area of investigation, a causal relationship has never been demonstrated. A reduction in rhinosinusitis symptoms following reduction in allergen exposure is not surprising in patients with CRS and allergic rhinitis. However, a recent analysis of home mold

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exposure found no difference in exposure levels between patients with AFRS and controls with atopic CRSwNP, which suggests that mold exposure levels may not be a key driver in development of AFRS.<sup>14</sup>

In summary, the absence of convincing evidence after more than two decades of investigation suggests that the hypothesis of fungi playing a major role in the pathophysiology of CRS in general has not been accepted; future research may identify genetic traits, or its interplay with environmental factors in CRSwNP disease evolution.

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Dr Asif H Khan reports being an employee of Sanofi, during the conduct of the study and may hold stock and/or stock options.

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