Allergic diseases and fungal exposome: prevention is better than cure

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Fungal exposure can result in a wide spectrum of diseases from infections to intoxication and allergy. The burden of fungal diseases has long been neglected and includes not only individual and societal impacts in terms of morbi-mortality but also major healthcare costs. The global burden of allergic broncho-pulmonary aspergillosis (ABPA) could probably exceeds 4.8 million people worldwide (given its high frequency in the India sub-continent), but prevalence field studies on allergic fungal diseases such as ABPA or severe asthma with fungal sensitization (SAFS; also called "fungal asthma") are few (1). Knowledge of which airborne fungi, determination of the fungal exposome and fungal disease itself are all necessary to optimize diagnosis and management. Joana Vitte and colleagues propose a very informative review in this issue summarizing fungal allergic diseases and the unmet needs for diagnosis and management (2). Among them, the authors underline the significance of fungal sensitization on lung function and its prevalence, and call for optimization of measurement tools from standard culturomic to high-throughput biological and biostatistical methods.

Because fungal exposome is universal, including not only indoor and outdoor air but also our microbiota, we must prioritize research in this topic in the 21st century to intelligently fight both direct but also indirect

impacts of fungal exposure. In particular evaluation of prevention strategies should be a cornerstone for a better outcome of fungal respiratory diseases that should be considered both by public health, but also in planning and optimizing the indoor built environment. Recent awareness of the strong links between *Aspergillus* airway infection/colonization and/or sensitization and asthma severity and exacerbations, COPD exacerbations and bronchiectasis, worse lung function in CF patients and after tuberculosis, some or all of which could be amenable to antifungal therapy, or prevented or improved with exposure reduction.

Two major prevention strategies for allergic fungal respiratory diseases may be identified (Fig. 1):

(i) Environmental prevention . Multiple and repeated exposures to fungal exposome may contribute to sensitization, fungal asthma and an increase in severe asthma-related complications (3). Environmental prevention has been demonstrated to prevent the onset of asthma and secondary prevention can ameliorate asthma symptoms and prevent exacerbations. Most individuals spend more than 50% of their time at home and so minimizing dampness and fungal growth at home will improve health and quality of life for chronic respiratory diseases (4). The value of home interventions implemented by trained healthcare workers and combining both education-based methods and a global allergen avoidance method may offer an opportunity for control of asthma severity for some patients, but prospective multicentric randomized studies are still needed (5-6). In a similar way, identification and minimization of at-risk exposures during school or work remains an active prevention strategy for workers to improve quality of life and save healthcare costs. Of course, air pollution control is an additional and mandatory challenge, for all countries.

(ii) Pharmacological prevention with antifungals and/or biologics. There are many indirect data indicating that early recognition and management of exacerbation or relapse during ABPA, SAFS or even chronic pulmonary aspergillosis can delay the onset of bronchiectasis and chronic complications. Thus, an appropriate antifungal treatment and maintenance therapy acting as secondary prophylaxis is a good strategy to limit relapses and irreversible sequelae. However, the scarce randomized clinical trials that evaluated different approaches of maintenance therapy during ABPA or SAFS such as oral azoles or nebulized liposomal-amphotericin B showed only trends of clinical improvement (7-8). Of note, delayed occurrence of exacerbation or relapse, or reduction of the number of exacerbation episodes are clinical elements of major importance regarding patient comfort and disease stability. The variability of individual response to long term maintenance antifungal therapy creates clinical equipoise for further research. Identification of outcome criteria such as disease stabililty rather than cure, and quality of life rather than quantitative endpoints might be considered. Besides, one challenge in real life conditions will be to select the optimal antifungal drug and delivery system on a case-by-case basis based on the structure of the underlying lung, the comorbidities of the patient, and the pharmacological properties each. The goal to reach is a target concentration in the different lung compartments such as lung tissue, walls of cavity, fungus ball or epithelial cells, with very different penetration between relatively avascular areas to mucus and lipid-rich membranes of host cells. New antifungal drugs and especially the new route of administration via nebulization are in clinical development and have differing chemical and physical attributes resulting in high local concentration, prolonged lung retention, slow absorption and low plasma concentrations. There are three companies developing inhaled azole antifungals currently. Topical antifungal therapy is attractive as it minimizes the potential of systemic toxicity, avoiding significant drug-drug interaction, while maximizing exposure in the lung. Finally, another pharmacological prevention of recurrent exacerbations could rely on anti-IgE or anti-Th2 biologics (10). At present, there are few data and no comparative randomized studies on prolonged treatment of ABPA or SAFS with biologics. Further randomized trials are needed in order to evaluate the efficacy and safety of such long term (and often expensive) biologics treatments, that could be avoided with prevention or lower cost antifungals.

Primary and secondary prophylaxis are more elegant approaches than cure. Modern environmental considerations and new promising antifungal drugs and monoclonal antibodies give hope for more improved clinical outcomes for those in need. Evaluation of preventive strategies is surely an essential unmet need against fungal exposome!

Conflicts of interest.

JPG: reports having received speaker fees, fees for board memberships and travel support from Gilead, MSD and Pfizer; Grant to the University Hospital of Rennes from the "Programme Hospitalier de Recherche Clinique Interrégional" 2013-2020 of the French Ministry of Health for ECENVIR study.

CG reports having received speaker fees, travel support from Pfizer, MSD; fees for board memberships from SOS Oxygène and Pulmatrix; grant support from Ohre Pharma, Pfizer, MSD, SOS Oxygène, ISIS Medical, Vivisol, Elivie, and AstraZeneca. Material and logistics support to all participating centres for NEBULAMB study from the firm PARI GmbH France. Grant to the University Hospital of Poitiers from the "Programme Hospitalier de Recherche Clinique Interrégional" 2012 of the French Ministry of Health for NEBULAMB study and 2017 for CPAAARI study.

DWD and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company, and share options in TFF Pharma. He acts or has recently acted as a consultant to Pulmatrix, Pulmocide, Biosergen, TFF Pharmaceuticals, Bright Angel Therapeutics, Pfizer, Omega, Novacyt and Cipla. He sits on the DSMB for a SARS CoV2 vaccine trial. In the last 3 years, he has been paid for talks on behalf of Hikma, Gilead, BioRad, Basilea, Mylan, Biorad and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group and recently joined the One World Guideline for Aspergillosis."

Author's contribution. JPG, CG and DWD: conceptualization and writing original draft.

Legend Figure 1. Fungal exposome impacts on lungs and strategies of prevention of allergic fungal diseases. ABPA: allergic broncho-pulmonary aspergillosis ; SAFS: severe asthma with fungal sensitization.

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