

Bioaerosols and sick building syndrome: particles, inflammation, and allergy

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Purpose of review

Sick building syndrome is a poorly understood condition that can be vexing to clinicians and public health investigators alike. Concerns about possible causes have recently shifted to bioaerosols, especially indoor mold contamination. Recently, controversy over the health effects of indoor bioaerosols has intensified in the media and in medical forums. Allergists and other clinicians are increasingly being asked to evaluate cases of sick building syndrome attributed to bioaerosol exposure. Although allergy may play a role, it is unlikely to fully explain the nonspecific symptoms of the condition. This review of recent literature will attempt to put into context the roles of allergy and nonallergic mechanisms in sick building syndrome.

Recent findings

Epidemiological and toxicological studies have provided further evidence of a possible link between bioaerosol exposure and sick building syndrome, but continue to have methodological limitations. Cross-sectional studies of building occupants have found associations between bioaerosols and symptoms of the condition, but case definitions and exposure assessment remain problematic. Attempts to develop better exposure assessment and biomonitoring methods have made limited progress. Toxicological studies of inhalation of bioaerosols continue to indicate potential toxicity, but at doses that are not comparable to human exposures indoors.

Summary

Epidemiological studies suggest an association between bioaerosols and sick building syndrome, and toxicological studies have provided some evidence supporting biological plausibility. However, the extent to which bioaerosol exposure may explain the nonspecific symptoms of the condition is unclear. Nonspecific inflammatory responses to bioaerosols, modified by psychosocial factors such as stress, may be a promising area for continued research.

Keywords

bioaerosols, building-related illness, inflammation, sick building syndrome, stress

Abbreviations

BRI	building-related illness
MVOC	microbial volatile organic compound
SBS	sick building syndrome

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Introduction

Symptoms and disease from indoor air exposures have been a public health concern since the 1970s. Sick building syndrome (SBS), also known as nonspecific building-related illness [1], refers to constellations of symptoms associated with occupancy of particular offices, homes and other nonindustrial buildings, for which no definite cause can be identified. SBS is often distinguished from building-related illness (BRI), in which symptoms can be explained by specific medical diagnoses such as allergy, asthma, infection, or a recognized toxic exposure (e.g. carbon monoxide). The diverse symptoms of SBS include mucous membrane irritation, headaches, fatigue, cognitive complaints, nausea, skin rash, and dizziness [2,3]. Lower respiratory symptoms may be included, although the extent to which these symptoms may be explained by specific pathology such as asthma exacerbation is often unclear. A number of occupant exposures have been implicated in SBS, such as numerous low-level chemical air contaminants, poor ventilation, physical conditions such as temperature and humidity, and psychological and social factors that may relate to stress, workplace organization, and job satisfaction [4]. In the past few years, the attribution of SBS to dampness and bioaerosols has become widespread [5,6]. Bioaerosols are defined as airborne particles that are living, or that originate from, living organisms. Fungal spores and fragments have been the major focus, but other bioaerosols associated with excessive building dampness and moisture, such as bacteria and dust mites, may also play some role in SBS. This review focuses on papers published since January 2003 that have addressed microbial aspects of indoor air quality and their relationship to SBS.

Controversy: mycotoxicosis and sick building syndrome

An intense controversy over the relationship between indoor bioaerosols and the 'nonspecific' illness symptoms of SBS continued over the review period. Citing a dearth of well conducted studies, a 2004 Institute of Medicine

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report concluded that available evidence did not support associations between dampness and fatigue and other nonspecific symptoms that have been attributed to mold, but that such associations could not be ruled out [7^{••}]. Others have called into question the validity of symptom-based illnesses ascribed to mold exposure [8[•]].

The role of fungal toxic metabolites (mycotoxins) in BRI and SBS has been at the center of the controversy. Fungi and bacteria, including some species found indoors, can produce toxins that have been isolated and are known to cause a wide range of toxic effects at sufficiently high doses. An American College of Occupational and Environmental Medicine evidence-based statement (2003) estimated that inhalation of a toxic dose of mycotoxins from spores in indoor air was improbable [6[•]]. In contrast, recent reports of several large case series suggested that mold and mycotoxin exposure caused clinically significant neurotoxic and immunotoxic effects [9[•]–11[•]]. Meanwhile, widespread public concern and litigation involving claims of personal injury caused by ‘toxic mold’ have become common in the US [12[•]].

Sick building syndrome and allergy

Against this backdrop of controversy and contention, allergists and occupational and environmental medicine specialists are increasingly being asked to evaluate and manage cases of building-related illness. SBS is a diagnosis of exclusion, and in clinical practice as well as in research, it may be challenging to distinguish SBS from BRI. For example, nonspecific mucosal irritation symptoms may clinically resemble mild specific allergy, and these conditions may overlap in the same individual. Allergy is a possible risk factor for increased nonspecific symptoms. In a recent controlled exposure study, patients with allergic rhinitis had increased sensitivity to irritation from a volatile organic compound [13[•]]. A large survey found that office workers with allergy were about twice as likely to report general symptoms [14[•]]. Few studies of associations between bioaerosols and SBS have attempted to systematically exclude upper respiratory allergy or asthma exacerbation as a cause for observed symptoms. The lack of standardization as well as variability of fungal extracts for mold allergy testing [15^{••}], and cross-reactivity between species [16], hampers efforts to either confirm or exclude mold allergy. However, given the predominance of nonspecific symptoms in affected individuals, it is unlikely that a majority of SBS cases are substantially explained by allergy.

Epidemiology

Epidemiological evidence for an association between bioaerosol exposure and SBS has come mainly from cross-sectional studies and investigations of ‘sick buildings’ that have found associations between symptoms and exposure to bioaerosols [17–19]. Recent studies have

extended this literature. In a synthesis of 80 problem-building investigations, observed risk factors for potential microbiologic contamination, such as water damage and poor drainage in ventilation systems, were associated with increased risk of work-related lower respiratory symptoms, but the study lacked any direct measurement of exposure to bioaerosols or potential confounders [20^{••}]. In a 1-year longitudinal panel study of 98 workers in four office buildings, nonspecific symptoms were associated with total culturable fungi collected from office chairs [21^{••}]. In a study of a mold-contaminated school, children reported fewer respiratory symptoms, headache, and joint pains after remediation [22[•]]. However, in a study of employees involved with bottle recycling and glass breaking in liquor stores, general somatic symptoms were more strongly associated with job strain than with elevated personal particulate matter or endotoxin exposures [23[•]].

In addition to inherent methodological limitations of cross-sectional studies, the lack of standardized health assessments and problems with exposure assessment continue to make interpretations of available studies difficult. Since SBS is by definition based on subjective symptoms and measured by self-report, some observers are skeptical that it can ever provide a reliable endpoint for study [8[•]]. The fundamental lack of knowledge about the nature and pathogenesis of SBS makes exposure assessment for potential causative agents challenging, since the relevance of any of a number of possible agents and exposure-time windows are unknown. Building occupants are likely to be exposed to a mixture of bioaerosols and other environmental exposures, further complicating exposure and risk assessment. A few recent studies have attempted to address concerns about exposure assessment.

Assessing relevant exposures

For both clinicians and investigators, critical evaluation of possible associations between bioaerosols and SBS requires attention to two fundamental questions. Did an exposure to the agent(s) occur? What was the magnitude of the exposure? For exposures that can vary greatly over time, such as bioaerosols, estimating the magnitude of exposure requires consideration of not only the concentration or intensity of exposure at any given time, but also when, and for how long, exposures at various intensities may have occurred. The two general approaches to exposure assessment for bioaerosols are environmental sampling and biomonitoring. In addition to measurement of bioaerosols *per se*, related exposures to mycotoxins and microbial volatile organic compounds (MVOCs) have been considered.

Environmental sampling

Inhalation is presumably the most important route of exposure to indoor microbial contaminants, with skin contact or ingestion less likely to lead to significant

exposure. Ideally, exposure assessment of bioaerosols would be done with direct measurement of agents in the individual's breathing zone using portable personal sampling devices. However, this may not be economically or technically feasible for large or extended studies. Of the few studies of SBS that have assessed bioaerosol exposure in nonindustrial indoor environments, all have used less direct measures such as area air sampling, dust sampling, questionnaires, inspection, or putative biomarkers of exposure.

As the sources of bioaerosols are living organisms, their composition and concentration indoors can be highly variable over time and location, depending on poorly understood ecological conditions that may be influenced by temperature, humidity, surface moisture, season, and ventilation. In general, analysis of collected dust samples may be a reasonable surrogate measure for long-term average exposure, whereas area air sampling may be a better proxy for recent exposures that are relevant to acute symptom responses. Both of these approaches may play important roles in evaluation of bioaerosols and SBS, but their validity and reproducibility are shown to be limited. In a study of 745 German homes, high correlations for endotoxin and allergen levels were found between two dust samples from living room floors, but repeated measures of total viable spore counts were very weakly correlated [24[•]]. A study of 496 Boston homes found little correlation between concentrations of culturable fungi in dust and short-term air samples [25[•]]. Lacking direct long-term air sampling measurements, the authors could not compare either dust samples or short-term air samples to actual long-term average air levels. Earlier studies have found variability of up to several orders of magnitude in hourly and weekly sampling of indoor air for mold spores [26].

Biomonitoring

Validated methods for directly measuring biological markers of exposure to bioaerosols are yet to be developed. Increased mean levels of IgG, IgM and IgA against *Penicillium*, *Aspergillus*, and *Stachybotrys* species were measured in serum of 500 patients from three states exposed to molds in about 60 water-damaged buildings, but the comparability of controls was not established, and little useful exposure data were provided [27]. Other studies have suggested that IgG antibodies to fungal antigens in serum, a potential indirect marker of exposure, are poorly correlated with exposure to mold indoors. In a study that compared 19 teachers exposed to moisture damaged buildings and seven teachers from a control school, no differences in serum IgG to 20 common mold species were found [28[•]]. Indoor-outdoor ratios for *Penicillium*, *Cladosporium*, and total fungi were greater in the moisture-damaged schools, but many mold species were found in both schools, limiting the ability of the study to

test the discriminatory power of specific IgG. Results from this study were consistent with findings from a recent study in school children [29]. IgG to mold extract antigens may lack the sensitivity needed to detect low-level indoor exposures as well as the specificity needed to discriminate between various exposures to ubiquitous mold species, which may share common antigens. More study is needed to determine if IgG and other antibodies can be useful for quantitative assessment of mold or other bioaerosol exposures. Improved understanding of exposures and responses to indoor bioaerosols is essential for continued progress in evaluating the relationship between bioaerosols and SBS.

Assessment of mycotoxin exposure

Mycotoxins are low-molecular-weight, nonvolatile, fungal metabolites which pose a health risk to humans and animals, most often through contamination of food [30[•]]. Species of fungi capable of producing mycotoxins can grow indoors, and this has led to concern that mycotoxins may cause human health effects including SBS [31]. Mycotoxin production varies with a variety of environmental factors and life-cycle stages. The mere presence of fungi that produce toxins does not prove that occupants have been exposed to mycotoxins. For most mycotoxins, reliable analytical methods for measuring concentrations in environmental samples such as house dust are not available [30[•]]. A new candidate urinary biomarker for exposure to deoxynivalenol, a mycotoxin produced by some *Fusarium* species, joins available biomarkers for aflatoxin B1 and ochratoxin [30[•],32].

Microbial volatile organic compounds

In addition to mycotoxins, indoor fungi can produce a wide variety of MVOCs, including alkanes, alkenes, ketones, organic acids, and terpenes [33]. MVOCs have been implicated as a potential cause of the eye, nose, and throat irritation reported by occupants of buildings with mold growth or dampness [34], but levels of exposure indoors are typically much lower than those known to cause irritation [35]. Some MVOCs, such as terpenes, react readily with ozone, a common indoor air contaminant, to create a secondary organic aerosol containing irritating products that include hydroxyl radicals, aldehydes, carboxylic acids, and fine particles [36[•],37]. Animal studies found these products to be more irritating than their precursors [38]. However, in a recent controlled exposure experiment, we found that 2 h exposure to a secondary organic aerosol formed by reaction of a mixture of volatile organic compounds and ozone did not cause increased nasal irritation or markers of inflammation in human volunteers [39].

Toxicology

Available data on the toxicity of bioaerosols that may be found in indoor air come from studies of acute, high-dose

exposures in in-vitro and animal models, not the more relevant study of chronic exposure to lower concentrations. It has been suggested that microbial toxins may cause the nonallergic symptoms of SBS and other illnesses that have been linked to mold and damp building exposures. In a comparison of the production of pro-inflammatory mediators in mouse and human respiratory cell lines, the relative overall potency of the bacterial species that were studied (*Pseudomonas fluorescens*, *Streptomyces californicus*, *Bacillus cereus*) was greater than that of the fungal species (*Stachybotrys chartarum*, *Aspergillus versicolor*, *Penicillium spinulosum*) [40[•]]. These results suggest that perhaps more attention should be paid to bacteria as possible agents for symptoms related to damp buildings. In an earlier study, a single large dose of spores of *S. californicus*, a sporulating bacterium isolated from the air inside damp buildings, induced acute inflammatory changes in mouse lungs [41]. A recent study indicated that systemic immune system changes occurred at lower doses than pulmonary inflammation in mice after 6 weekly doses of *S. californicus* at lower concentrations [42[•]]. The ability of these or other extra-pulmonary effects of bioaerosols to explain the systemic symptoms of SBS remains to be seen, but the results indicate the need for further study of these effects at low doses of relevant bioaerosols.

In a study of relevance to the upper respiratory and mucous membrane irritation that is often prominent among SBS symptoms, 15 min inhalations of a nebulized *A. versicolor* extract caused sensory irritation in the 'Alarie' animal bioassay (ASTM E 981-84, 1984) [43]. Although the inhalation exposure in this study was more relevant than commonly used pulmonary instillation techniques, the relatively high doses of a mold extract were not comparable to indoor air exposures.

Conclusion

After two decades of study, conclusions about the etiology of SBS remain elusive. Whether the recent interest in bioaerosol exposure will ultimately lead to better understanding of SBS remains to be seen. The limited epidemiology of SBS, including a number of studies cited here, continues to suggest that it is a multifactorial condition in which a variety of biological, chemical, physical, and psychological factors can play a role [20^{••}, 21^{••}, 22[•], 23[•]]. The road to a better understanding of SBS may require resisting the tendency to dichotomize SBS as 'toxicological' versus 'psychological', by remaining open to hypotheses that cross the mind-body interface. For example, evidence from animal and human studies suggests that inflammatory stimuli and psychological stress can both lead to increased circulating proinflammatory cytokines that mediate systemic 'sickness behavior' symptoms like fatigue, cognitive dysfunction, lowered pain thresholds, nausea, and social withdrawal [44]. Whether or not

bioaerosols at levels of exposure found indoors, with or without psychological stress, can actually cause sufficient airway inflammation to trigger these 'acute phase responses' is unknown. Mounting evidence that relatively low levels of particulate matter air pollution can cause systemic effects such as increased cardiovascular mortality, possibly mediated by similar inflammatory mechanisms, provides an intriguing parallel [45]. Given the present limited understanding of bioaerosol, one can only speculate as to the relative toxic potency of bioaerosols and other common particulate matter exposures.

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