Review Article

Recognizing filamentous basidiomycetes as agents of human disease: A review

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Abstract

Filamentous basidiomycetes (BM) are common environmental fungi that have recently emerged as important human pathogens, inciting a wide array of clinical manifestations that include allergic and invasive diseases. We reviewed 218 reported global cases of BM fungi. The most common etiologic agent was Schizophyllum commune in 52.3% (114/218) of the cases followed by Hormographiella aspergillata (n = 13; 5.9%), Ceriporia lacerata (n = 11; 5%), and, rarely, Volvariella volvacea, Inonotus tropicalis, Irpex lacteus, Phellinus undulates, Perenniporia species, Bjerkandera adusta, Sporotrichum pruinoseus, Phanerochaete steroids, and Cyclomyces tabacinus. These fungi are present in the environment as gilled mushrooms, shelf fungi, and bracket fungi. However, in clinical settings, they usually present as nonsporulating white moulds that are difficult to identify. Moreover, the GenBank database of these fungi is limited. Regarding the country-wise distribution of cases, Japan topped the list with about 43% (n = 94) of globally reported cases, followed by India (57; 26%), the United States (4%), Austria (3.2%), Iran (3.2%), France (2.8%), and the remaining one-third from 16 other countries. The respiratory tract was the most commonly afflicted site (n = 71), with the majority of the cases (42; 59.1%) being allergic in etiology and comprising 34 cases of allergic bronchopulmonary mycosis. Also, B. adusta has been implicated in a recently described clinical entity, that is, fungus associated chronic cough, reported exclusively from Japan. BM fungi-incited diseases are currently underdiagnosed due to lack of awareness and expertise, warranting comprehensive epidemiological and susceptibility studies to determine their prevalence and to predict a more appropriate therapy.

Key words: filamentous basidiomycetes, antifungal susceptibility, sequencing, nonsporulating moulds.
Introduction

The incidence of human disease caused by environmental fungi has been on the rise. This is primarily attributed to risk factors such as the wide use of modern immunosuppressive drugs, invasive medical instrumentation, international travel, extreme weather, natural disasters, and large-scale usage ofazole antifungals in agriculture [1,2]. Many human pathogenic fungi such as Coccidioides, Histoplasma, Aspergillus, and Cryptococcus have their natural habitats in the natural environment; in many instances, the infecting fungal pathogens are acquired from the surrounding environment. Although an increase in fungal infections has been reported widely for these fungi, the potential of common environmental filamentous basidiomycetes (BM) as human pathogens has not been examined [3]. BM fungi have recently emerged as increasingly important pathogens that incite a wide array of clinical disease manifestations including invasive as well as noninvasive diseases [4]. In this review, we discuss BM fungi as agents of systemic mycoses, with special reference to allergic disease. We further describe the role of molecular techniques and variation in antifungal susceptibility profiles of the wide array of BM implicated in human diseases.

The phylum Basidiomycota, containing fungi colloquially known as mushrooms, is classified into three subphyla, 16 classes, and 52 orders [5]. The BM fungi encountered in clinical settings are conventionally classified into Agaricales and Stereales. They display macroscopically visible fruiting bodies recognizable as gilled mushrooms, toad stools, and coral fungi in the latter in their natural habitat [6]. Some BM propagate sexually through the development of specialized club-shaped reproductive structures called basidia; others reproduce asexually. Under laboratory conditions, BM from clinical specimens usually present as nonsporulating moulds that grow as cottony white colonies [7,8]. Furthermore, most clinical isolates are monokaryons, neither clamps nor fruiting structures are produced. Thus, the lack of phenotypic characteristics and absence of sporulation render the identification of BM fungi difficult in standard microbiology laboratories [9,10]. Occasionally, spicules, hyphal pegs, clamp connections, arthroconidia, and/or chlamydoconidia, which distinguishes BM fungi from other classes of hyaline fungi, are observed [4,9]. However, morphological identification fails to identify with certainty the species of BM that are implicated in a given infection. Consequently, inconclusive culture reports adversely affect treatment decisions. Notwithstanding the fact that nonsporulating BM fungi such as Hormonaphiella aspergillata and Volvariella volvacea are reported to be resistant to many antifungals such as amphotericin B, caspofungin,itraconazole, voriconazole, and posaconazole, their specific identification in unique clinical settings cannot be emphasized [11–14]. Furthermore, breakthrough infections due to H. aspergillata in patients receiving caspofungin either as prophylaxis or therapy for various fungal infections are a matter of concern [14]. The specific and thorough identification of BM implicated in these breakthrough infections is mandatory for successful therapeutic outcome of these patients [4].

Conventional identification

Morphologically, it is difficult to identify white, woolly colonies of BM. However, colonies that (may) emit an unpleasant odor, are susceptible to cycloheximide, and are tolerant of the fungicide benomyl (2–10 µg/ml) are possibly BM and should be investigated further [4,9]. Among all of their microscopic features, clamp connections are considered characteristic for BM and may be observed in as many as 78% of clinical isolates specifically in Schizophyllum commune and Ceriporia lacera [4]. The “clamp connection” refers to a hyphal bridge between two cells, directed to facilitate the transfer of daughter nuclei and resulting in a dikaryon [3] (Fig. 1). As mentioned above, most clinical isolates of BM fungi, particularly S. commune, are monokaryons. Dikaryotization can be achieved in these isolates by simple mating experiments that use another monokaryon along with the test strain, resulting in development of clamp connections [9]. A selective agar medium containing ligin, guaiacol, and benomyl, which reduces growth of other moulds and allows detection of laccase or peroxidase-producing BM, has been used for primary isolation of saprophytic BM from soil [15]. A distinct red zone of oxidized guaiacol is observed beneath the BM colonies due to the action of laccase or peroxidase after 2 weeks of incubation [15]. In clinical settings, Sabouraud glucose agar (SGA) containing benomyl, a selective fungicide to which many BM show some degree of tolerance but to which most ascomycetes are sensitive, has been reported to facilitate isolation of BM fungi from clinical specimens [9]. Further, induction of fruiting bodies such as basidiocarps (mushrooms) may be successful in some isolates of S. commune by exposure of the culture plate to alternate cycles of light and dark for several weeks [8,9]. Chowdhary et al. [16] observed that formation of basidiocarps occurred in only 4 of 26 isolates of S. commune using alternate cycles of light and dark. Moreover, it was possible to induce characteristic fruiting bodies in other BM fungi, by inoculating thick suspensions of BM on autoclaved decayed wooden bark pieces of Syzygium cumini (blackberry tree, Jambu) and twigs of Quercus acutissima (sawtooth oak), which provide the natural environment for sporulation.
However, the induction of sporulation is time consuming and requires an additional 4–6 weeks after isolation of BM in culture.

**Molecular identification**

The specific identification of clinically significant moulds entails the use of DNA-based methods. In most cases, this involves sequencing of the ribosomal internal transcribed spacer (ITS) and D1/D2 larger subunit (LSU) of the ribosomal DNA (rDNA) regions \[4,15,17,18\]. Sequencing of the rDNA ITS region may offer a match in GenBank, leading to an increased number of taxa being reported in the medical literature \[21\]. Singh et al. \[4\] recently characterized 52 nonsporulating fungi isolated from respiratory specimens using both ITS and D1/D2 region sequencing and identified 92% of the isolates. Similarly, the use of both ITS and D1/D2 region sequencing provided higher identification rates of 99.4% in the study by Romanelli et al. \[19\] who analyzed 169 BM fungi. However, Pounder et al. \[22\] observed lower rates (79%) of BM identification based on ITS region sequencing alone in 50 nonsporulating moulds. Furthermore, specific species identification using both the ITS and D1/D2 region sequences in the GenBank database showed inconcordant results \[4,19\]. This was noted by Romanelli et al. \[19\], who compared BLAST (basic local alignment search tool) results in the GenBank database of 168 ITS and D1/D2 region sequences and observed that only 28% revealed same species identification. They further reported that there were no entries in GenBank for 14% of the top ITS hits and 16% of the top D1/D2 hits. Notably, only 30% of the BM fungi had either an ITS or a D1/D2 sequence deposit in GenBank, but not both \[19\]. Similarly, this discrepancy of missing sequences of either ITS or D1/D2 for the given BM species was noted by Singh et al. \[4\]. The authors reported that only 69.2% of the BM isolates were identified by ITS sequencing and the majority (92%) by D1/D2 sequencing \[4\]. Furthermore, 5.7% of BM could be identified only to the taxon Basidiomycota \[4\]. Moreover, sequence lengths of both the ITS and the D1/D2 regions deposited in GenBank are incomplete or largely truncated. Notably, only 8% of the ITS region and 10% of the D1/D2 region of BM fungi had complete sequence data in GenBank \[19\]. Furthermore, not only is the GenBank database limited \[4,19\], multiple different species of BM fungi share the same percent identity due to low genetic variations in the region chosen for sequence identification. Therefore, there is a need for stringent quality control of the GenBank database. This can be achieved by implementing strategies that restrict submission of sequences with adequate length for both the ITS and LSU regions.

**Filamentous basidiomycete fungi**

The specific morphological features of BM fungi implicated in human mycoses are discussed below followed by an analysis of the disease entities associated with these
fungi. The globally reported cases of BM fungi are summarized in Table 1 [4,12–14,16,17,23–56]. Table 2 [4,12–14,16,17,37,38,42,50,51,56] depicts the available antifungal susceptibility data of these fungi.

**Schizophyllum commune**

*Schizophyllum commune* is the most common mushroom or shelf fungus belonging to the order Agaricales. It is ubiquitous in the environment on dead and decaying organic matter, especially the rotten wood of trees [7]. It is the most common BM reported from human infections, ranging from allergic respiratory conditions to severe life-threatening brain lesions in both immunocompetent and immunocompromised hosts. Recently, Chowdhary et al. [8] reviewed 71 globally reported cases of diseases caused by *S. commune*. The respiratory tract was involved in the majority of cases, comprising 63% of cases of bronchopulmonary diseases and 31% of sinusitis. Notably, only four cases with extrapulmonary infections were observed, comprising one each of onychomycosis, brain abscess, meningitis, and palate ulceration [57–60]. Subsequent to this review, 43 new cases were reported during 2012–2013; these are listed in Table 1 [16,23–32]. Of these 43 cases, 14 (32.55%) were allergic bronchopulmonary mycosis (ABPM) and 8 (18.6%) were sinusitis [4,23,24,26–30,32]. The enhanced recognition of *S. commune* in clinical settings shows the growing knowledge and awareness for this BM among clinicians and mycologists.

**Morphological and molecular identification**

*Schizophyllum commune* appears as hyaline, septate, and nondichotomously branching hyphae in direct potassium hydroxide wet mounts of clinical samples. In most instances, the fungus grows at 28°C and 37°C on SGA supplemented with 10 µg/ml of benomyl as sterile white colonies with woolly texture. The strains of *S. commune* produce a distinctive bleach-like odor and some produce crystals in culture plates [9]. The monokaryotic strains of *S. commune* are devoid of the characteristic spicules or clamp connections and do not form basidiocarps that contain basidiospores (sexual spores) [8,9]. However, Chowdhary et al. [4,16] studied their sporulation pattern using alternate cycles of light and dark, induction performing experiments on potato dextrose agar and on twigs of *S. cumini*. They observed fan-shaped basidiocarp formation, with basidiospores in 4 of 26 *S. commune* isolates after 3–4 weeks at 28°C. However, for specific identification, sequencing of ITS and D1/D2 regions is mandatory [19,20].

**Antifungal susceptibility testing**

Barring a study by Chowdhary et al. [16], the information on antifungal susceptibility of *S. commune* isolates is mostly restricted to individual isolates. The authors reported data on *in vitro* antifungal susceptibility of 30 isolates of *S. commune* strains isolated from patients with respiratory diseases. They reported low geometric mean minimal inhibitory concentrations (MICs) of isavuconazole (0.19 µg/ml), itraconazole (0.2 µg/ml), voriconazole (0.24 µg/ml), and amphotericin B (0.29 µg/ml) and high geometric mean MICs of fluconazole (19 µg/ml) and fluconazole (17 µg/ml) [16]. Similarly, González et al. [61] reported the lowest geometric mean MICs of itraconazole, voriconazole, posaconazole, and amphotericin B for five strains of *S. commune* (Table 2).

**Hormographiella aspergillata**

The genus *Hormographiella*, described by Guarro et al. [62] in 1992, include three species: *H. aspergillata*, *H. verticillata*, and *H. candelabra*. *Hormographiella aspergillata* is the asexual form (anamorph) of *Coprinus cinereus*, which was recently renamed as *Coprinopsis cinerea* [63]. This species of the basidiomycetous mushroom genus occurs commonly in compost and sewage. The spores of this pathogen are abundant in the environment, and the fungus grows well at 37°C [62]. *Hormographiella aspergillata* is recognized as an agent of invasive infections in immunosuppressed patients [34,38]. Such cases are anecdotal, described mainly in patients with hematological malignancies, mostly in patients with neutropenia or after hematopoietic stem cell or bone marrow transplantation (Table 1) [12,14,34–40]. Also, a breakthrough infection of *H. aspergillata* in a neutropenic French patient who was receiving caspofungin therapy has been documented, highlighting the cautionary usage of caspofungin in high-risk patient populations [39].

**Morphological and molecular identification**

The fungus grows as white to cream-colored, dense, cottony colonies on SGA plates at 28°C and 37°C [62]. Microscopically hyaline, septate conidiophores bearing conidiogenous hyphae that disarticulate into rectangular and round-ended arthroconidia may be observed [62]. The fruiting bodies are normally absent, and often clamp connections are missing in culture [11]. Also, the shape of the arthroconidia is non-diagnostic. Therefore, definitive identification of the fungus requires sequencing of the ITS region of the ribosomal DNA [11].

**Antifungal susceptibility testing**

The antifungal susceptibility data for this fungus are derived from sporadic case reports and high *in vitro* MICs of fluconazole (8–256 µg/ml), 5-flucytosine (8–256 µg/ml) and caspofungin (2–32 µg/ml) have been reported [14,37,38].
<table>
<thead>
<tr>
<th>Fungi (n)</th>
<th>Country (n)</th>
<th>Diagnosis (n)</th>
<th>Underlying conditions/symptoms</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Year [Ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophyllum commune (71 + 43)*</td>
<td>India (36)</td>
<td>Sinusitis (1)</td>
<td>Diabetic; nasal obstruction, discharge, and disturbed vision</td>
<td>FESS</td>
<td>Not mentioned</td>
<td>2012 [23]</td>
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<tr>
<td></td>
<td>AFRS (1)</td>
<td>Sneezing, bilateral nasal obstruction, purulent discharge</td>
<td></td>
<td>Intranasal polypectomy</td>
<td>Cured</td>
<td>2013 [24]</td>
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<tr>
<td></td>
<td>Keratitis (1)</td>
<td>Pain, redness, watering in the left eye</td>
<td></td>
<td>VRC with systemic therapy of oral ketoconazole, therapeutic keratoplasty</td>
<td>Increased infiltrates and graft failure at 3 months</td>
<td>2013 [25]</td>
</tr>
<tr>
<td></td>
<td>ABPM (12)</td>
<td>–</td>
<td></td>
<td>Inhaled corticosteroids and/or LABA and oral steroids in 6 patients and ITC or VRC in 2 patients</td>
<td>1 lost to follow-up, 7 attained remission</td>
<td>2013 [16]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fungal pneumonia (4)</td>
<td></td>
<td>VRC in 2 patients</td>
<td>Resolution (1), death (2), death before treatment (1)</td>
<td>2013 [4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fungal ball (3)</td>
<td>–</td>
<td>VRC or ITC in 2 patients and observation in 1 patient</td>
<td>All stable</td>
<td></td>
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<tr>
<td></td>
<td>AFRS (2)</td>
<td>–</td>
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</tr>
<tr>
<td></td>
<td>Colonizer (12)</td>
<td>–</td>
<td>Oral and inhaled corticosteroids with or without LABA</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>South Korea (2)</td>
<td>AFRS (1)</td>
<td>Nasal block, anterior purulent rhinorrhea</td>
<td>FESS, topical and systemic steroids</td>
<td>Cured</td>
<td>2012 [26]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sino-orbital infection (1)</td>
<td>Left proptosis and left-sided facial paresthesia</td>
<td>Endoscopic biopsy of the left maxillary sinus mucosa and an incisional biopsy of the orbital mass with L-AMB and VRC</td>
<td>Cured</td>
<td>2012 [27]</td>
</tr>
<tr>
<td></td>
<td>Japan (3)</td>
<td>ABPM (2)</td>
<td>Productive cough with abnormal pulmonary infiltrates</td>
<td>Mucus plugs removed with bronchoscope</td>
<td>No recurrence after 4 years of follow-up</td>
<td>2011, 2012 [28,29]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Productive cough, fever, malaise, and abnormal pulmonary infiltrates</td>
<td>ITC and bronchoscopic suctioning and flushing</td>
<td>No recurrence after 6 months of follow-up</td>
<td></td>
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<tr>
<td></td>
<td>Sinusitis (1)</td>
<td></td>
<td>ALL; allogeneic bone marrow transplantation, fractionated total body irradiation, cord blood transplant; fever, right periorcular pain and swelling</td>
<td>L-AMB and VRC</td>
<td>Cured</td>
<td>2013 [30]</td>
</tr>
<tr>
<td>Fungi (n)</td>
<td>Country (n)</td>
<td>Diagnosis (n)</td>
<td>Underlying conditions/symptoms</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Year [Ref]</td>
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<tr>
<td>China (1)</td>
<td></td>
<td>Empyema thoracis (1)</td>
<td>History of pulmonary tuberculosis, chronic obstructive pulmonary disease, hypertension, congestive heart failure, fever, productive cough, dyspnea for 2 months</td>
<td>Multiple image-guided drainages and VRC</td>
<td>Died</td>
<td>2013 [31]</td>
</tr>
<tr>
<td>Austria (1)</td>
<td></td>
<td>Sinusitis and brain abscess (1)</td>
<td>Diabetes mellitus; headache</td>
<td>External surgical lancing of the right frontal sinus and abscess drainage; intracerebral lancing of abscess formations and FESS of the left sinus frontalis, L-AMB and oral POS</td>
<td>Cured</td>
<td>2013 [32]</td>
</tr>
<tr>
<td>Hormographiella aspergillata (13)</td>
<td>United Kingdom (1)</td>
<td>Endocarditis (1)</td>
<td>Treated for bacterial endocarditis</td>
<td>–</td>
<td>Died while undergoing cardiopulmonary bypass</td>
<td>1971 [33]</td>
</tr>
<tr>
<td>The Netherlands (1)</td>
<td>Pulmonary infection (1)</td>
<td>AML and pleuritic chest pain</td>
<td>AMB desoxycholate, ITC</td>
<td>Died with respiratory failure</td>
<td>1997 [12]</td>
<td></td>
</tr>
<tr>
<td>Germany (1)</td>
<td>Pulmonary infection (1)</td>
<td>AML, bone marrow transplant</td>
<td>AMB and fluconazole</td>
<td>Died from circulatory failure</td>
<td>1997 [34]</td>
<td></td>
</tr>
<tr>
<td>Belgium (2)</td>
<td>Pulmonary infection (2)</td>
<td>Malignant T lymphoblastic type non-Hodgkin’s lymphoma, with neutropenic episode</td>
<td>AML with allogeneic peripheral blood stem cell transplantation and febrile neutropenia</td>
<td>AMB desoxycholate</td>
<td>Stable</td>
<td>2002 [35]</td>
</tr>
<tr>
<td>United States (1)</td>
<td>Disseminated infection (1)</td>
<td>AML, allogeneic human leucocyte antigen–matched bone marrow transplant</td>
<td>CAS</td>
<td>Died from respiratory failure and refractory septic shock</td>
<td>2005 [36]</td>
<td></td>
</tr>
<tr>
<td>Switzerland (3)</td>
<td>Disseminated infection (1)</td>
<td>AML with second T-cell replete transplant and febrile neutropenia</td>
<td>IV VRC and oral POS followed by CAS</td>
<td>Died with cerebellar hemorrhage</td>
<td>2010 [38]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary infection (2)</td>
<td>AML with cord-blood transplantation</td>
<td>IV VRC and high-dose IV L-AMB</td>
<td>Persistent nodules in both lungs; died from multiorgan failure</td>
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<td></td>
<td>Pulmonary infection (2)</td>
<td>AML, febrile neutropenia, nonproductive cough</td>
<td>Pulmonary nodules were operatively removed; IV VRC, oral POS and high-dose IV AMB</td>
<td>Died from AML disease progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France (3)</td>
<td>Pulmonary infection (3)</td>
<td>Biphenotypic acute leukemia, with persistent fever</td>
<td>CAS with VRC, later L-AMB</td>
<td>Cured</td>
<td>2011 [14]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>X-linked adrenoleukodystrophy; underwent allogeneic stem cell transplantation; febrile neutropenia</td>
<td>CAS and L-AMB</td>
<td>Died from multiorgan failure</td>
<td></td>
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<tr>
<td><strong>Fungi</strong> (n)</td>
<td><strong>Country</strong> (n)</td>
<td><strong>Diagnosis</strong> (n)</td>
<td><strong>Underlying conditions/symptoms</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Outcome</strong></td>
<td><strong>Year [Ref]</strong></td>
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<tr>
<td>ALL, neutropenia</td>
<td>VRC, L-AMB</td>
<td>Cured</td>
<td>2012 [39]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary and skin infection (1)</td>
<td>AML, stem cells transplanted, lesions on right forearm.</td>
<td>CAS, L-AMB, VRC; surgical resection of the lesion</td>
<td>Died from respiratory failure and septic shock</td>
<td>2013 [40]</td>
<td></td>
<td></td>
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<tr>
<td>Ceriporia lacerata (11)</td>
<td>Fungal pneumonia (6)</td>
<td>–</td>
<td>ITC or VRC (2)</td>
<td>Lost to follow-up (3); resolution (2); died (1)</td>
<td>2013 [4, 17]</td>
<td></td>
</tr>
<tr>
<td>Austria (1)</td>
<td>Colonizer (5)</td>
<td>–</td>
<td>–</td>
<td>Stable (4); deterioration due to unrelated causes (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (11)</td>
<td></td>
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<tr>
<td>Ceriporia lacerata (11)</td>
<td>India (11)</td>
<td>Fungal pneumonia (6)</td>
<td>–</td>
<td>ITC or VRC (2)</td>
<td>Lost to follow-up (3); resolution (2); died (1)</td>
<td>2013 [4, 17]</td>
</tr>
<tr>
<td>Colonia lacerata</td>
<td>Austria (1)</td>
<td>Pulmonary and skin infection (1)</td>
<td>–</td>
<td>ITC or VRC (2)</td>
<td>Lost to follow-up (3); resolution (2); died (1)</td>
<td>2013 [4, 17]</td>
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<td>Colonia lacerata</td>
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<td>India (11)</td>
<td>Fungal pneumonia (6)</td>
<td>–</td>
<td>ITC or VRC (2)</td>
<td>Lost to follow-up (3); resolution (2); died (1)</td>
<td>2013 [4, 17]</td>
<td></td>
</tr>
<tr>
<td>Volvariella volvacea (1)</td>
<td>United States (1)</td>
<td>Invasive disease (brain) (1)</td>
<td>Stage IV nodular sclerosing Hodgkin’s lymphoma, double umbilical cord blood transplantation, cardiogenic shock.</td>
<td>VRC with L-AMB</td>
<td>Died</td>
<td>2011 [13]</td>
</tr>
<tr>
<td>Inonotus tropicalis (1)</td>
<td>United States (1)</td>
<td>Invasive mycoses (1)</td>
<td>X-linked chronic granulomatous disease</td>
<td>Surgical excision, AMB with VRC and later CAS</td>
<td>Residual inflammation after 3 years; initiation of triple antifungal therapy</td>
<td>2005 [41], 2007 [42]</td>
</tr>
<tr>
<td>Phellinus undulates (1)</td>
<td>New Zealand (1)</td>
<td>Soft-tissue infection (1)</td>
<td>Type 2 diabetic, end-stage renal disease secondary to diabetic nephropathy; hypertension and ischemic heart disease</td>
<td>Surgical excision</td>
<td>Cured</td>
<td>2011 [43]</td>
</tr>
<tr>
<td>Bjerkandera adusta (58)</td>
<td>Japan</td>
<td>Bronchial asthma and hypersensitivity pneumonitis (1)</td>
<td>Bronchial asthma, sinobronchial syndrome, and yellow nail syndrome</td>
<td>Environmental control measures and oral prednisolone (20 mg/day)</td>
<td>Cured</td>
<td>2009 [44]</td>
</tr>
<tr>
<td>Fungus-associated chronic cough (5+12+17+13+10)</td>
<td>Chronic intractable cough, harboring BM fungi in sputum</td>
<td>ITC 50 mg/day for 14–21 days and or nebulized AMB (1 ml of 2.5 mg/ml solution) once or twice a week</td>
<td>Favorable response in resolution of cough</td>
<td>2009 a, b, c, 2011, 2013 [45–49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perenniporia (2)</td>
<td>India (1) Fungal ball (1)</td>
<td>Chronic pulmonary infection (1)</td>
<td>Lung abscess (3)</td>
<td>Dyspnea, cough with scanty expectoration and edema in both legs, history of hysterectomy</td>
<td>Not mentioned</td>
<td>1966 [52]</td>
</tr>
<tr>
<td>Thailand (1)</td>
<td>Invasive pulmonary infection (1)</td>
<td>Dyspnea, cough with scanty expectoration and chest pain</td>
<td>–</td>
<td>–</td>
<td>1988 [53]</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Fungi (n)</th>
<th>Country (n)</th>
<th>Diagnosis (n)</th>
<th>Underlying conditions/symptoms</th>
<th>Treatment</th>
<th>Year [Ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclomyces tabacinus (1)</td>
<td>Australia (1)</td>
<td>Pulmonary infection (1)</td>
<td>Not mentioned –</td>
<td>Surgical excision; IV VRC followed by oral VRC for 2 months</td>
<td>1992 [54]</td>
</tr>
<tr>
<td>Irpex lacteus (1)</td>
<td>Austria (1)</td>
<td>Soft-tissue infection (1)</td>
<td>Not mentioned –</td>
<td>IV, intravenous</td>
<td>2006 [55]</td>
</tr>
<tr>
<td>Ceriporia lacerata</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2005 [56]</td>
</tr>
</tbody>
</table>

71 cases of S. commune have been reviewed earlier by Chowdhary et al., reference no. [8] and only additional cases after their review are discussed here.

ABPM, allergic bronchopulmonary mycosis; AFRS, allergic fungal rhinosinusitis; ALL, acute lymphoblastic leukaemia; AMB, amphotericin B; AML, acute myeloid leukaemia; CAS, caspofungin; FESS, functional endoscopic sinus surgery; ITC, itraconazole; IV, intravenous; L-AMB, liposomal amphotericin B; LABA, long-acting β agonists; POS, posaconazole; SLE, systemic lupus erythematosus; VRC, voriconazole.

However, variable activity with MICs in the range of 0.03 to 4 µg/ml, 0.06 to 1 µg/ml, 0.03 to 32 µg/ml, and 0.125 to 2 µg/ml were observed for amphotericin B, voriconazole, itraconazole, and posaconazole, respectively [12,14, 36–38].

Ceriporia lacerata

*Ceriporia lacerata*, which is ubiquitous in the environment, is a wood-inhabiting white rot fungus. It was first isolated in 1994 from decayed wood in the Miyazaki forest in Japan [18]. *Ceriporia lacerata* characteristically produce white to buff, dense nonsporulating colonies. [18]. The fungus has been implicated in a wide spectrum of clinical manifestations ranging from saprobi colonizing to fungal pneumonia [4].

Morphology and molecular identification

Microscopically, this fungus appears as hyaline, septate hyphae usually without clamp connections and spicules and with oblong-ellipsoid to ellipsoid basidiospores [17]. Few members of this group sporulate on special media. Chowdhary et al. [17] studied the induction of basidiocarp formation on different media with periodic exposure to light and observed formation of brain coral-shaped basidioecarp in one of four isolates after 4 weeks of incubation. Singh et al. [4] reported in vitro susceptibility data of 11 isolates of this fungus and observed low MICs of itraconazole, voriconazole, posaconazole, isavuconazole, and amphotericin B, whereas high MICs were reported for fluconazole and 5-flucytosine. Also, high MICs were observed for the echinocandins [4]. As with other BM fungi, definitive identification requires sequencing.

Volvariella volvacea

*Volvariella volvacea*, commonly known as paddy straw mushroom, is a tropical and subtropical saprophytic fungus that belongs to the family Amanitaceae, which is prevalent in Southeast Asia and Africa [63]. It has been cultivated as a delicacy in the southern provinces of China [63]. To date, only a one case of invasive disseminated infection has been reported. It involved the brain of an Indian female umbilical cord blood transplant recipient from the United States [13].

Morphological and molecular identification

The fungus grows at 40°C on SGA and other standard media. Typically, nonsporulating aerial and substrate hyphae and oblong to globose chlamydospores occur singly or in chains; they develop a copper to brown color and become thick walled after prolonged incubation. The final identification of *V. volvacea* in the above-mentioned
Table 2. Global data on *in vitro* antifungal susceptibility profile of filamentous basidiomycetous fungi (1996–2013).

<table>
<thead>
<tr>
<th>Fungi tested (n)</th>
<th>Methods applied for antifungal susceptibility testing</th>
<th>MIC Parameters</th>
<th>MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
</tr>
<tr>
<td><em>Schizophyllum commune</em></td>
<td>CLSI</td>
<td>GM</td>
<td>0.06</td>
</tr>
<tr>
<td>N = 5</td>
<td></td>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>0.06–0.125</td>
</tr>
<tr>
<td>N = 30</td>
<td>CLSI</td>
<td>GM</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
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<td></td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>0.03–8</td>
</tr>
<tr>
<td><em>Bjerkandera adusta</em></td>
<td>CLSI</td>
<td>GM</td>
<td>0.11</td>
</tr>
<tr>
<td>N = 14</td>
<td></td>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
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<td></td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>0.06–0.25</td>
</tr>
<tr>
<td><em>Ceriporia lacerata</em></td>
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<td>GM</td>
<td>0.147</td>
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<td>N = 11</td>
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<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>0.06–0.5</td>
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<tr>
<td><em>Homographiella aspergillata</em></td>
<td>Broth microdilution</td>
<td>Range</td>
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<tr>
<td>N = 5</td>
<td></td>
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<td>N = 1</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>N = 1</td>
</tr>
<tr>
<td></td>
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<td>N = 1</td>
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<tr>
<td>Fungi tested (n)</td>
<td>Number of strains tested</td>
<td>Methods applied for antifungal susceptibility testing</td>
<td>MIC (µg/ml) Parameters</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Posaconazole</td>
<td>-</td>
<td>-</td>
<td>6</td>
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<tr>
<td>Amphotericin B</td>
<td>-</td>
<td>-</td>
<td>16–64</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>-</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>Micafungin</td>
<td>-</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>-</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>-</td>
<td>-</td>
<td>8–32</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>-</td>
<td>-</td>
<td>8–32</td>
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<td>Itraconazole</td>
<td>-</td>
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<td>0.03–0.25</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
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<td>Isavuconazole</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>-</td>
<td>-</td>
<td>0.125</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>-</td>
<td>-</td>
<td>0.25</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Micafungin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>-</td>
<td>-</td>
<td>16–64</td>
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<tr>
<td>Flucytosine</td>
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<td>-</td>
<td>64–128</td>
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</tr>
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<td>Voriconazole</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Posaconazole</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>-</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>-</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>Micafungin</td>
<td>-</td>
<td>-</td>
<td>32</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>-</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>-</td>
<td>-</td>
<td>128–256</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>-</td>
<td>-</td>
<td>256–512</td>
</tr>
<tr>
<td>Volvariella volvacea (1)</td>
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<td>-</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
</tr>
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<td>Voriconazole</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>-</td>
<td>-</td>
<td>0.125</td>
</tr>
<tr>
<td>Amphotericin B</td>
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</tr>
<tr>
<td>Caspofungin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Micafungin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>-</td>
<td>-</td>
<td>128–256</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>-</td>
<td>-</td>
<td>256–512</td>
</tr>
<tr>
<td>Perenniporia spp. (2)</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>-</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>-</td>
<td>-</td>
<td>32</td>
</tr>
<tr>
<td>Micafungin</td>
<td>-</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>-</td>
<td>-</td>
<td>128</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>-</td>
<td>-</td>
<td>256–512</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>-</td>
<td>-</td>
<td>512–1024</td>
</tr>
</tbody>
</table>

AFG, Anidulafungin; CLSI, Clinical Laboratory Standard Institute; GM, geometric mean; MFC, Micafungin; MIC, minimum inhibitory concentration.
case was achieved by sequencing the ITS and D1/D2 region of ribosomal DNA [13]. The in vitro antifungal susceptibility data for a single isolate showed resistance to many antifungals compared with other BM species, which may have therapeutic implications. The echinocandins fluconazole and 5-flucytosine had no activity against this fungus. Also, high MICs of posaconazole and voriconazole were observed [13].

**Inonotus tropicalis and Phellinus undulates**

The two genera *Inonotus* and *Phellinus* in the family Hymenochaetaeae are wood-decaying fungi that are associated with white rot decay of various woody angiosperms; they exhibit worldwide distribution [64]. *Phellinus* is distinguished from *Inonotus* by its hard, woody, perennial fruiting bodies and dimitic hyphal system. In contrast, *Inonotus* produces softer, annual fruiting bodies with a monomitic hyphal system. The three types of hyphal systems include monomitic, dimitic, and trimitic. When the basidioma consists exclusively of degenerative hyphae, the hyphal system is monomitic. In addition to the generative hyphae, the dimitic hyphal system consists of any other type of hyphae (either skeletal or binding hyphae). When all three types of hyphae are present, the hyphal system is trimitic. Generative hyphae are first-formed, thin-walled branched hyphae that are produced directly from secondary hyphae and possess clamp connections. The other types of hyphae, namely, the skeletal and binding hyphae, originate as specialized branches of the generative hyphae. The skeletal hyphae are thick walled without clamp connections and serve as strengthening structures, providing rigidity to the basidioma. Binding hyphae, also called ligative hyphae, are thick walled and lack clamp connections.

Phylogenetic analysis based on nuclear LSU sequences of *Phellinus* and *Inonotus* transferred *P. tropicalis* into the *Inonotus sensu stricto* clade [65]. *Inonotus tropicalis* has been implicated in invasive infections in patients with chronic granulomatous diseases [41,42], whereas a solitary case of cutaneous infection due to *Phellinus undulatus* in a diabetic patient is on record [43].

**Perenniporia species**

*Perenniporia* belong to the order Poriales, family Agaricomycetes. The members of the genus *Perenniporia* are ubiquitous in the environment and grow as saprobes on dead wood by decomposition of lignin and cellulose, leading to white rot [66,67]. They are characterized by formation of porate, often resupinate fruiting bodies that are flat on the substrate, with the hymenium on the outer side on rotten branches. Fruiting bodies with pores or tubes on the underside are defined as porate fruiting bodies. The fungus appears as white, cottony colonies at 28°C and 37°C. The first case of human disease was reported from India where a *Perenniporia* sp. was responsible for an intrapulmonary fungal ball that produced recurrent hemoptysis [50]. A case of invasive pulmonary mycosis was reported recently in Thailand [51].

**Sporotrichum pruinosum**

*Sporotrichum pruinosum*, the anamorph of *Phanerochaete chrysosporium*, is a ubiquitous saprobic basidiomycetous mould found in soil and materials composed of cellulose [68]. Although this BM has not been directly implicated in invasive infections, its role in pulmonary infections seems likely, as demonstrated by its repeated isolation from respiratory specimens of patients, some of whom also had type I cutaneous immune response against this pathogen [53]. Furthermore, the fungus incited pulmonary lesions in experimentally infected mice, indicating its pathogenic potential [53]. Similar to other BM colonies on SGA, the fungus grows as white, powdery mycelia, attaining a diameter of 40–45 mm in 3 days at 25°C. The species is characterized by the formation of aleurioconidia and arthroconidia in young cultures; large, thick-walled, globose

**Bjerkandera adusta**

*Bjerkandera adusta* is a polypore basidiomycete that forms fruiting bodies with pores or tubes on the underside. It is widely found on dead deciduous trees in North America. However, all clinical cases of this fungus have originated from Japan [45–49]. *Bjerkandera adusta* has been implicated as the agent responsible for fungus-associated chronic cough in comprehensive studies reported by Ogawa et al. [45–49] and also for bronchial asthma and hypersensitivity pneumonitis in a solitary case [44]. The fungus is characterized by rapid growth with yellowish-white to tan, dense, woolly or cottony colonies. Arthroconidia are produced by schizolytic dehiscence of undifferentiated branched or unbranched hyphae and are thin walled. Chlamydospores may be observed, and clamps are usually lacking.
chlamydospores are observed in standard culture media such as SGA at 37°C and 25°C [53,68]. The abundant chlamydospinid and rapid growth at 37°C are features of this fungus. Interestingly, the chlamydospinid wall in vitro in experimentally infected mice was thicker than that found in vitro at 25°C or 37°C, which may represent an attempt by the fungus to resist host defense mechanisms [53]. No data on in vitro antifungal susceptibility of these BM fungi are available.

**Cyclomyces tabacinus**

*Cyclomyces tabacinus* is a bracket fungus belonging to the family Hymenochaetaceae; it is found on dead tree trunks and conifers in tropical to subtropical regions [69,70]. A single report of deep tissue infection in a dairy farmer who developed cystic lesions on the anterior tibial tendon was reported from Australia [55]. The characteristic microscopic feature of the genus *Cyclomyces* is the presence of brown setae or modified terminal hyphae lining the pores [55]. *Cyclomyces tabacinus* isolated from the clinical case showed dagger-shaped setae (hypidia) containing a bright orange–brown cytoplasm [55].

**Irpeps lacteus**

*Ireps lacteus* is a wood-rotting bracket mushroom belonging to the family Hymenomycetes that is distributed worldwide. Microscopically, no specific features are observed and definitive identification requires ITS and LSU region sequencing. A solitary case of *I. lacteus* pulmonary infection in a 9-year-old child with acute lymphoblastic leukemia who was treated successfully with amphotericin B has been reported [56].

In addition, other BM fungi such as *Marasmiellus palnivorus* and *Porostereum spadiceum* have also been isolated from respiratory secretions of patients with chronic respiratory disorders [4]. However, the pathogenic potential of these BM is yet to be established.

**Spectrum of disease**

As discussed above, the spectrum of disease caused by filamentous BM is varied and ranges from asymptomatic saprobic colonization, fungal balls, and allergic respiratory mycoses such as allergic fungal sinusitis and ABPM to invasive systemic mycoses such as fungal pneumonias, fungemia, and brain abscesses [4]. Additionally, the role of BM in mycotoxicosis and shiitake dermatitis is well known, though a detailed discussion of these disease entities is beyond the scope of this review; the reader is referred to recent updates on these subjects [71–73].

**Colonization of the respiratory tract**

No specific criteria exist to define “colonization,” but filamentous BM may be considered colonizers in patients without an obvious allergic or invasive mycosis, the respiratory secretions of which yield a fungal agent [74]. Although this definition has been proposed in the context of *Aspergillus* spp., it may not be inappropriate to use this definition for other fungi. Like other fungi, BM are known to colonize the respiratory tract of individuals with anatomical lung damage or seemingly normal lungs. BM fungi such as *S. commune*, *C. lacerata*, *B. adusta*, and *Perenniporia* have been reported to colonize respiratory tracts of patients with underlying conditions including chronic sinusitis, chronic obstructive pulmonary diseases, interstitial lung disease, posttubercular sequelae, and asthma [4,23,26,44]. Although most instances of colonization go unnoticed and may be discovered incidentally [4,17,75,76], there are occasions when respiratory symptoms could be attributed to the colonization [8,9,50]. The enigmatic cases of bronchial mycoid impaction from Japan typify such an instance where *S. commune* was associated with symptomatic airway colonization [77–79]. Particularly well known among colonizers are cases of fungal balls arising within preexisting lung cavities, usually resulting as a sequel to pulmonary tuberculosis. To date, four cases of intracavitary pulmonary mycetomas due to *S. commune* and a solitary case due to a *Perenniporia* species have been documented [4,8,50]. The fungal ball cases include two additional cases reported subsequent to the review by Chowdhary et al. [8]. Such a lesion may lie quiescent and, more often than not, leads to recurrent episodes of hemoptysis, thus prompting medical attention. Another interesting association of the colonized state seen with fungal balls is the development of allergic reactions to fungal antigens. It is postulated that the constant exposure of the respiratory tract to fungal antigens released from the mycetoma sensitizes the individual. Conversely, a mycetoma may develop de novo in an allergic individual colonized by the fungus [80]. Although more widely studied in the case of the Aspergilli, such an association may not be totally unlikely in the case of BM, as in the case of *S. commune* [8,53]. Generally, no specific treatment is warranted in order to eliminate colonization; however, invasion could occur in immunocompromised individuals [4,17,74].

**Allergic diatheses**

The allergic diatheses are probable the most widely reported of all basidiomycotic manifestations in humans. The allergic affliction of the upper and lower respiratory tract occurs in the classically described forms, namely, allergic fungal rhinosinusitis (AFRS) and ABPM, respectively. *Schizophyllum commune* predominates, with 34 cases of ABPM reported
to date, of which 20 have been reviewed by Chowdhary et al. [4,81]. In addition, S. commune has also been shown to be responsible for atopic asthma; however, as opined by the authors, the same could probably be the serological variant of ABPM [28]. Nevertheless, it would be erroneous to assume that S. commune is the only agent responsible for allergic respiratory manifestations. Although not reported or studied as extensively as S. commune, other BM fungi have been documented as agents of allergic fungal disease. Earlier studies have demonstrated the incidence of basidiomycota-caused allergy to range from 3.5% [82] to 25.4% [83]. Of all the BM, Psilocybe cubensis, Pleurotus ostreatus, Ganoderma meredithae, Coprinus quadrifidus, Pleurotus pulmonalis, Coprinus comatus, and Boletus edulis have been positively associated with atopic respiratory diseases [82,83]. In 1988, Khan et al. [53] presented three cases from which Sporotrichum pruinosum was isolated from respiratory specimens as a potential pathogenic agent. Two of these patients were notable because they showed type 1 cutaneous hypersensitivity to S. pruinosum. However, the definitive diagnosis of an ABPM could not be proven, probably having been overshadowed by the concurrent diagnosis of allergic bronchopulmonary aspergillosis.

Allergic affliction of the upper respiratory tract manifests as AFRS. The pathogenic process that leads to AFRS is essentially the same as for ABPM [84]. No fewer than five cases of AFRS caused by S. commune have been reported to date [8,23,26]. A recent addition to the range of AFRS is Phanerochaete velutina, reported by Ogawa et al. [85]. The spectrum of fungus-associated allergic respiratory diseases has been further expanded by Ogawa et al. [44,45,48,86]. These authors have extensively studied the role that BM fungi play in the pathogenesis of intractable cough. They have categorized patients with fungus-associated chronic idiopathic cough, based on the differences in symptomatology and myco-allergological findings, into those sensitized to basidiomycetes, in particular, B. adusta, and those not sensitized but only harboring the mould [45]. Consequently, a new disease concept—fungus-associated chronic cough (FACC)—has been proposed for such a group of patients. The disease is characterized by the manifestation of chronic cough, presence of environmental fungi, in particular BM fungi in the sputum, and a good clinical response to antifungal drugs. FACC also encompasses the syndrome of allergic fungal cough [46]. Thus, where the role of BM fungi as allergens in chronic cough seems certain, it remains to be ascertained if such a phenomenon is exclusive to B. adusta.

The treatment of fungus-associated respiratory disorders has classically been the systemic use of steroids, with an aim to achieve remission in disease activity, which is monitored subjectively through the patients’ symptoms and objectively by reduction in the serological markers of disease activity. However, the prolonged use of systemic steroids can lead to unacceptable toxicity. Another option that has shown some promise as an alternative to steroids is antifungal treatment. The principle of such therapy is to prevent/reduce fungal colonization of the airways. Although no guidelines exist on the use of this therapy, favorable results have been noted in patients with ABPM [16,77,87], allergic asthma [85], and FACC [46,49]. With regard to the treatment of AFRS, a wide array of options, ranging from local toileting to surgical intervention with or without the use of steroids and antifungals, has been used [23,88].

Invasive fungal mycoses

Filamentous BM have been found to be responsible for invasive infections in varied human hosts. This review (Table 1) revealed that no fewer than 74 reported cases of invasive mycoses were due to BM, of which 34 cases of invasive mycoses due to S. commune have been reviewed by Chowdhary et al. [8]; the remaining 40 cases are presented in Table 1. The lungs were the most frequently involved organ in invasive fungal disease, being involved in up to 29 of all reviewed cases [4,12,14,17,23,25,27,30–43,51–56]. The lungs is probably the most well-known BM pathogen responsible for human disease. The risk factors responsible for invasive infections caused by BM fungi were similar to those for other invasive mycoses, such as leukemias, recipients of hematopoietic stem cell transplants, immunodeficiency states, uncontrolled diabetes mellitus, prolonged corticosteroid usage, cancer chemotherapy, and underlying structural lung damage. The therapeutic options used to treat invasive diseases are presented in Table 1 and include conventional antifungal agents such as amphotericin B, caspofungin, voriconazole, itraconazole, and posaconazole. Although most fungi were found to be sensitive to commonazole antifungals with the exception of fluconazole, variable success rates could be due to the baseline differences in patient characteristics and severity of the predisposition.

Finally, notwithstanding the fact that although BM fungi are being increasingly recognized in clinical specimens, their definitive species identification using conventional methods remains a challenge. Thus, these pathogens are underrecognized due to the lack of molecular identification facilities in most developing countries. Consequently, in most cases,
the true burden of the diseases caused by these fungi has yet to be discovered.

Declaration of interest

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