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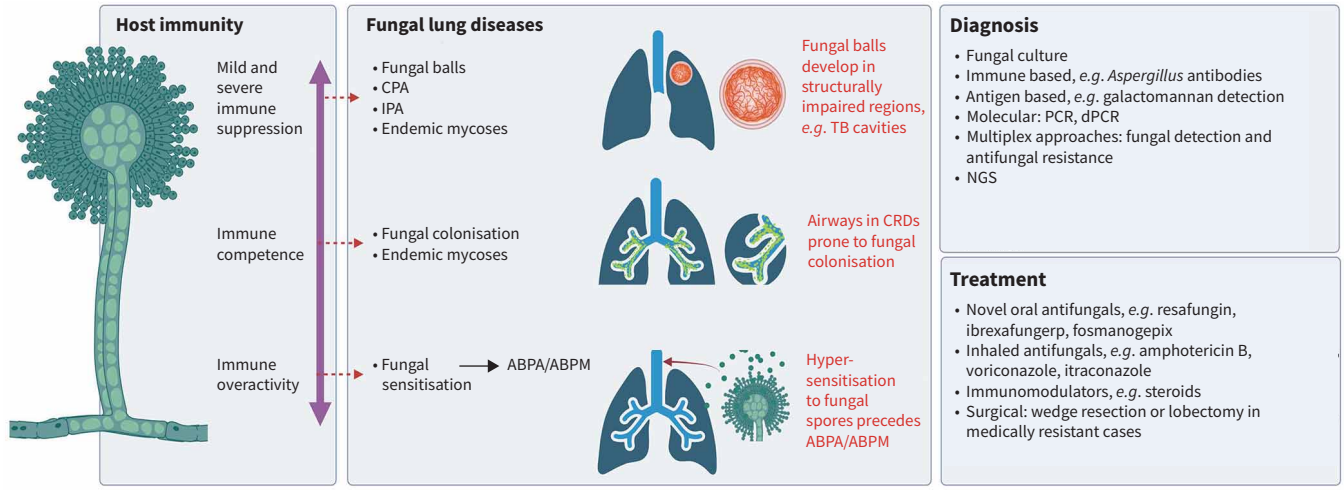

GRAPHICAL ABSTRACT Relationship of fungal lung disease with host immunity, diagnosis and treatment options. CPA: chronic pulmonary aspergillosis; IPA: invasive pulmonary aspergillosis; ABPA: allergic bronchopulmonary aspergillosis; ABPM: allergic bronchopulmonary mycosis; TB: tuberculosis; CRD: chronic respiratory diseases; dPCR: digital PCR; NGS: next-generation sequencing. Figure created with Biorender.com.

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Fungal lung disease occurs independently or complicates underlying lung disease. Type and severity are determined by host immunity, geography and environment. Next-generation sequencing is revolutionising diagnostic and treatment strategies. https://bit.ly/3TFwAJ3

Cite this article as: Jaggi TK, Agarwal R, Tiew PY, *et al*. Fungal lung disease. *Eur Respir J* 2024; 64: 2400803 [DOI: 10.1183/13993003.00803-2024].

Received: 28 April 2024
Accepted: 13 Sept 2024

Abstract

Fungal lung disease encompasses a wide spectrum of organisms and associated clinical conditions, presenting a significant global health challenge. The type and severity of disease are determined by underlying host immunity and infecting fungal strain. The most common group of diseases are associated with the filamentous fungus *Aspergillus* species and include allergic bronchopulmonary aspergillosis, sensitisation, aspergilloma and chronic and invasive pulmonary aspergillosis. Fungal lung disease remains epidemiologically heterogenous and is influenced by geography, environment and host comorbidities. Diagnostic modalities continue to evolve and now include novel molecular assays and biomarkers; however, persisting challenges include achieving rapid and accurate diagnosis, particularly in resource-limited settings, and in differentiating fungal infection from other pulmonary conditions. Treatment strategies for fungal lung diseases rely mainly on antifungal agents but the emergence of drug-resistant strains poses a substantial global threat and adds complexity to existing therapeutic challenges. Emerging antifungal agents and increasing insight into the lung mycobiome may offer fresh and personalised approaches to diagnosis and treatment. Innovative methodologies are required to mitigate drug resistance and the adverse effects of treatment. This state-of-the-art review describes the current landscape of fungal lung disease, highlighting key clinical insights, current challenges and emerging approaches for its diagnosis and treatment.

Introduction

Fungal lung disease has been increasing in past decades and represents a unique challenge to clinicians worldwide. The spectrum of clinical disease is diverse, ranging from hypersensitivity to colonisation to invasive illness, some with high mortality, with continuing barriers to accurate and prompt diagnostics and limited treatment options. Furthermore, a single patient can "move" between disease states over time, depending on changes to their underlying immunity. With climate change and ageing populations, the array of potential fungal pathogens and associated resistance continues to grow and the increasing use of immunosuppressive or immunomodulating therapies has expanded the "at-risk" patient population.

The intricate relationship between host immune status and fungal infection plays a key role in determining the risk, onset, presentation, course and outcome in all forms of fungal lung disease, exemplified by

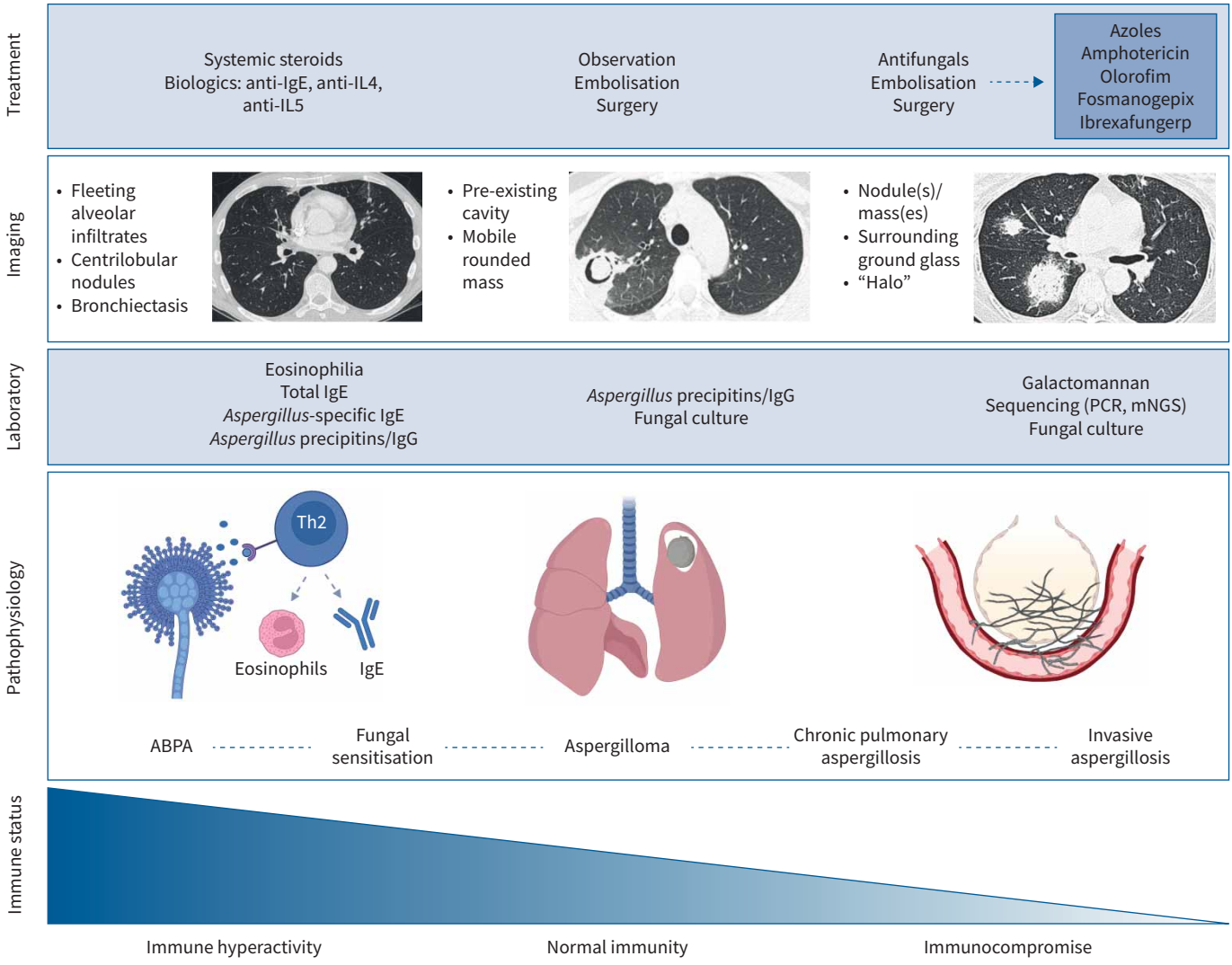

FIGURE 1 Schematic overview of the clinical spectrum of *Aspergillus*-associated disease with accompanying relationship to host immune status, radiographic findings, diagnostics and treatment modalities. IL: interleukin; mNGS: metagenomic next-generation sequencing; ABPA: allergic bronchopulmonary aspergillosis; Th2: T-helper type 2. Figure created with Biorender.com.

Aspergillus-associated disease (figure 1). The role of host immunity is important in understanding pathogenesis, achieving diagnosis and selecting treatment for patients, with those immunocompromised at highest risk of invasive disease [1]. Even mild immune alterations, such as those observed in several chronic respiratory disease (CRD) states, predispose to fungal colonisation, allergy and subsequent infection [1–3]. While *Aspergillus* species are well-recognised causes of fungal lung disease, non-*Aspergillus* fungi also play a significant role in pulmonary infections. These include a diverse array of pathogens such as *Candida*, *Cryptococcus* and *Pneumocystis*, but include endemic fungi such as *Histoplasma*, *Coccidioides* and *Blastomyces* that can cause severe lung disease, particularly in the immunocompromised patient, presenting unique diagnostic and therapeutic challenges.

In this state-of-the-art review, we describe the current landscape of fungal lung disease, highlighting clinical features and the complex relationship to underlying host immunity. We explore current challenges and evaluate emerging, promising approaches for improved diagnosis, including molecular approaches, metagenomic next-generation sequencing (mNGS) and advances in treatment.

Fungal lung disease and immune competence

Individuals with CRDs are prone to fungal colonisation [4–10]. The wide range of reported prevalence (3–57%) is in part due to the varied approaches to detection (culture or PCR) and differing definitions of

colonisation, some based on a single sample and others on a series of consecutive samples, demonstrating persistence [4–21]. *Aspergillus fumigatus* and *Candida albicans* remain the commonest fungi isolated in CRDs, with key risks for detection including inhaled corticosteroid and antibiotic use, prior exacerbations and isolation of *Pseudomonas* [5–8, 13, 22, 23]. There is geographic variability in *Aspergillus* colonisation, with *A. fumigatus* the most common species identified and variable prevalence reported in India, Spain, Iran and the UK [6, 21, 24–26], while in the Himalayas, increases in *A. flavus* were noted in patients with CRDs [27]. In cystic fibrosis (CF), *A. fumigatus* colonisation downregulates the expression of the vitamin D receptor, leading to enhanced T-helper 2 (Th2) inflammation [28]. Treatment with itraconazole reduced *Aspergillus* burden and Th2 responses, improving symptoms and radiology [28]. Importantly, however, randomised controlled trials evaluating the effect of itraconazole in *A. fumigatus*-colonised CF have demonstrated unfavourable outcomes, although such trials were limited by small numbers and low detectable therapeutic levels of itraconazole [13, 29]. While the specific role of *Aspergillus* colonisation is less studied in other CRDs, emerging evidence suggests that an evolution from colonisation to *Aspergillus*-associated disease exists, including sensitisation, allergic bronchopulmonary mycosis (ABPM), allergic bronchopulmonary aspergillosis (ABPA) and invasive aspergillosis, with implications for lung function, exacerbations and mortality in asthma and COPD [5, 7, 17, 19, 30, 31]. Increased sputum cell counts and neutrophilic inflammation are associated with *Aspergillus* detection in COPD, while in bronchiectasis, *Aspergillus* colonisation is prevalent and geographically variable, with *A. fumigatus* and *A. terreus* the most common species identified [32]. *A. fumigatus* is predominant in Asia (*i.e.* Singapore and Malaysia) while *A. terreus* is more prevalent in the UK (*i.e.* Dundee, Scotland) [32]. Enhanced systemic chitinase activity, involved in host defence, is detectable in *Aspergillus*-colonised bronchiectasis and is associated with exacerbations [33–35]. Taken together, collective evidence supports a potentially deleterious effect of *Aspergillus* airway colonisation; however, it remains uncertain if such colonisation drives disease progression or represents a marker of severe disease. The lack of standardised protocols for the detection of airway fungi also likely underestimates the true prevalence of fungal colonisation in CRDs.

Aspergillus bronchitis is a lesser described entity characterised by a chronic superficial infection of the trachea and/or bronchial tree by *Aspergillus* [36]. Proposed diagnostic criteria include chronic respiratory symptoms accompanied by a positive sputum or bronchoalveolar lavage fluid (BALF) result for *Aspergillus*, determined by culture or PCR, and an elevated *Aspergillus* IgG serum level in the absence of other underlying fungal-related disease [36]. Characteristic features on bronchoscopy include mucoid impaction and local invasion by *Aspergillus* hyphae, with COPD and bronchiectasis as the most commonly associated comorbidities [36–38]. Patients should not meet criteria for other established fungal lung disease, particularly ABPA, because these characteristics are also observed in such patients [36]. In CF, *Aspergillus* bronchitis is reported in 9% of cases, with antifungal treatment showing efficacy in reducing symptoms and improving lung function [37, 39, 40]. Most studies on *Aspergillus* bronchitis remain limited, small and retrospective, and even if this clinical entity represents a distinct form of fungal lung disease, it warrants further evaluation.

Fungal lung disease and immune overactivity

Fungal sensitisation

Fungal sensitisation represents an important clinical state observed in individuals with chronic respiratory diseases and is characterised by elevated fungal-specific IgE and/or immediate cutaneous hypersensitivity to the respective fungal extract. *Aspergillus* sensitisation (AS) is most common and defined by an *Aspergillus*-specific IgE $\geqslant$0.35 kUA·L^{-1} (kilo units of antibody per litre) and/or immediate cutaneous hypersensitivity to *Aspergillus* extracts [41]. Prevalence of AS in asthma ranges from 5.4% to 16.9% in the community, rising to 25% in tertiary care [42–46]. Patients with severe asthma and AS are referred to as having severe asthma with fungal sensitisation (SAFS), an emerging severe asthma phenotype [41]. Recently, AS and ABPA have been described in COPD with a pooled prevalence of 9.5% [47, 48]. While some studies propose direct associations between AS and increased COPD exacerbation frequency, uncertainty remains about the benefits of antifungal treatment [18, 49]. AS precedes the development of ABPA, and although a quarter of asthma patients in tertiary care are sensitised to *A. fumigatus*, only a proportion develop ABPA (*i.e.* 37% of those sensitised) [42]. To prevent progression from AS to ABPA and then subsequent development of bronchiectasis, early evaluation for AS and ABPA is recommended for all asthma patients receiving tertiary care [50].

Allergic bronchopulmonary mycosis/allergic bronchopulmonary aspergillosis

ABPM is a complex group of lung disorders incited by immune overactivity against various fungi colonising the airways of patients with CRD, most commonly asthma or CF [51]. ABPA is a term reserved for disorders caused by *Aspergillus* species, while ABPM refers to instances of allergic mycoses resulting

from fungi other than *Aspergillus* [50]. Less commonly, ABPA complicates the disease course in other airway diseases including COPD and bronchiectasis, with especially high occurrence in those with concurrent bronchiectasis and COPD [52–55]. The incidence of ABPM is lower than that of ABPA, with most reported as case series [56]. ABPA remains an important cause, consequence and treatable trait in bronchiectasis owing to its treatment responsiveness, although recurrent and sometimes prolonged treatment courses may be required for some [57].

While not predominant in indoor or outdoor air, *A. fumigatus* is commonly involved in allergic mycoses due to the size of its conidia (2–3.5 µm) and thermotolerant nature facilitating entry and growth into the smallest airways [58]. Two key events in ABPA pathogenesis includes *Aspergillus* colonisation and a skewed type-2 immune response (figures 2 and 3) [59]. Both events are presumably genetically determined, because not all asthma patients develop ABPA despite comparable exposure to the same environment. The normal human host rapidly eliminates *A. fumigatus* by innate and adaptive immune mechanisms [60]. Polymorphisms in airway epithelial receptors, innate immune pathways (pattern recognition receptors: toll-like receptors, surfactant proteins, mannose-binding lectin *etc.*), major histocompatibility complex proteins and adaptive immune pathways (interleukin-4R, interleukin-13 *etc.*) prevent the elimination of *A. fumigatus* and promote the development of an aberrant type-2 immune response [61–63]. Eosinophils remain the primary mediators of inflammation in ABPA, with the interaction between eosinophils and *A. fumigatus* releasing galectin-10 and forming Charcot–Leyden crystals [64]. Subsequently, eosinophils undergo cell death forming histone-rich extracellular traps and increase the viscosity of mucus plugs, which in turn prevents the elimination of *A. fumigatus* and contributes to ABPA pathogenesis [65]. The prevalence and underlying predisposing factors for the occurrence of ABPA vary between different geographic regions. In a recent systematic review, the prevalence of ABPA in asthma (tertiary care) varied widely (0.8–70%) with a pooled prevalence of 11.3% [42]. In the only community study from North India, the prevalence of ABPA-complicating asthma was 5.7% [45]. Separately, in two large registry studies, ABPA was reported as a cause of bronchiectasis in 2.8% and 8.2% of cases, respectively [66, 67]. The occurrence of ABPA in CF varied widely between 3% and 25%, with a pooled prevalence of 8.9% [68]. Most ABPA patients present with refractory asthma; however, one fifth can have well-controlled asthma, requiring moderate-to-high doses of inhaled steroids.

Other important common manifestations of ABPA are fleeting radiological opacities, haemoptysis and mucus plug expectoration. The diagnosis of ABPA is based on a combination of clinical, radiological and immunological findings. The ABPA working group of the International Society for Human and Animal Mycology recently framed new guidelines for diagnosis (table 1) [50]. In an individual with a predisposing condition or compatible clinical presentation, it is essential to demonstrate AS (raised *A. fumigatus* IgE) and disease activity (raised serum total IgE). The presence of fungal-specific IgG, blood eosinophilia and consistent imaging confirm the diagnosis. ABPA is classified based on chest computed tomography (CT) as serological ABPA (ABPA-S) (ABPA without bronchiectasis), ABPA with bronchiectasis (ABPA-B), ABPA with mucus plugging (ABPA-MP), ABPA with high-attenuation mucus (ABPA-HAM) or ABPA with chronic pleuropulmonary fibrosis (ABPA-CPF). ABPA treatment tenets include anti-inflammatory agents: glucocorticoids and/or biological agents targeting type-2 immune responses to control inflammation; and antifungal agents (oral or nebulised) to decrease airway fungal colonisation. Asymptomatic ABPA is not routinely treated, and systemic therapy is only indicated in those with poor asthma control or recurrent exacerbations. Patients with acute ABPA (newly diagnosed or exacerbations) can be treated with oral glucocorticoids or itraconazole for 4 months [69, 70]. A combination of itraconazole and glucocorticoids is not recommended as first-line therapy for acute ABPA but reserved for treating recurrent (⩾2 in the past 1–2 years) ABPA exacerbations [71]. Oral voriconazole, posaconazole and isavuconazole are not first-line agents for acute ABPA [72]. Similarly, high-dose inhaled corticosteroids or biological agents should not be used as primary therapy for acute ABPA. Patients with treatment-dependent ABPA (*i.e.* ⩾2 ABPA exacerbations, each occurring within 3 months of stopping glucocorticoids, or worsening symptoms and imaging, or rise in total IgE by ⩾50% within 4 weeks of tapering oral steroids on two separate occasions) may be treated with long-term itraconazole, nebulised amphotericin B or biological agents targeting type-2 inflammation [73–78]. Importantly, patients should be followed up 8–12 weeks post treatment initiation, with treatment response indicated by improvement in symptoms (⩾50%) and imaging (significant improvement, ⩾50%), along with a ⩾20% reduction in total IgE (figure 3). Recently, significant treatment responses were observed with the following chest CT findings: extent and density of mucoid impaction, centrilobular micronodules, consolidation and bronchial wall thickening [79]. Almost 50% of patients experience ABPA exacerbations post treatment cessation [80]. ABPA exacerbations are characterised by a sustained worsening (⩾2 weeks) of respiratory symptoms or new opacities on chest imaging and an increase in total IgE by ⩾50% from periods of clinical stability

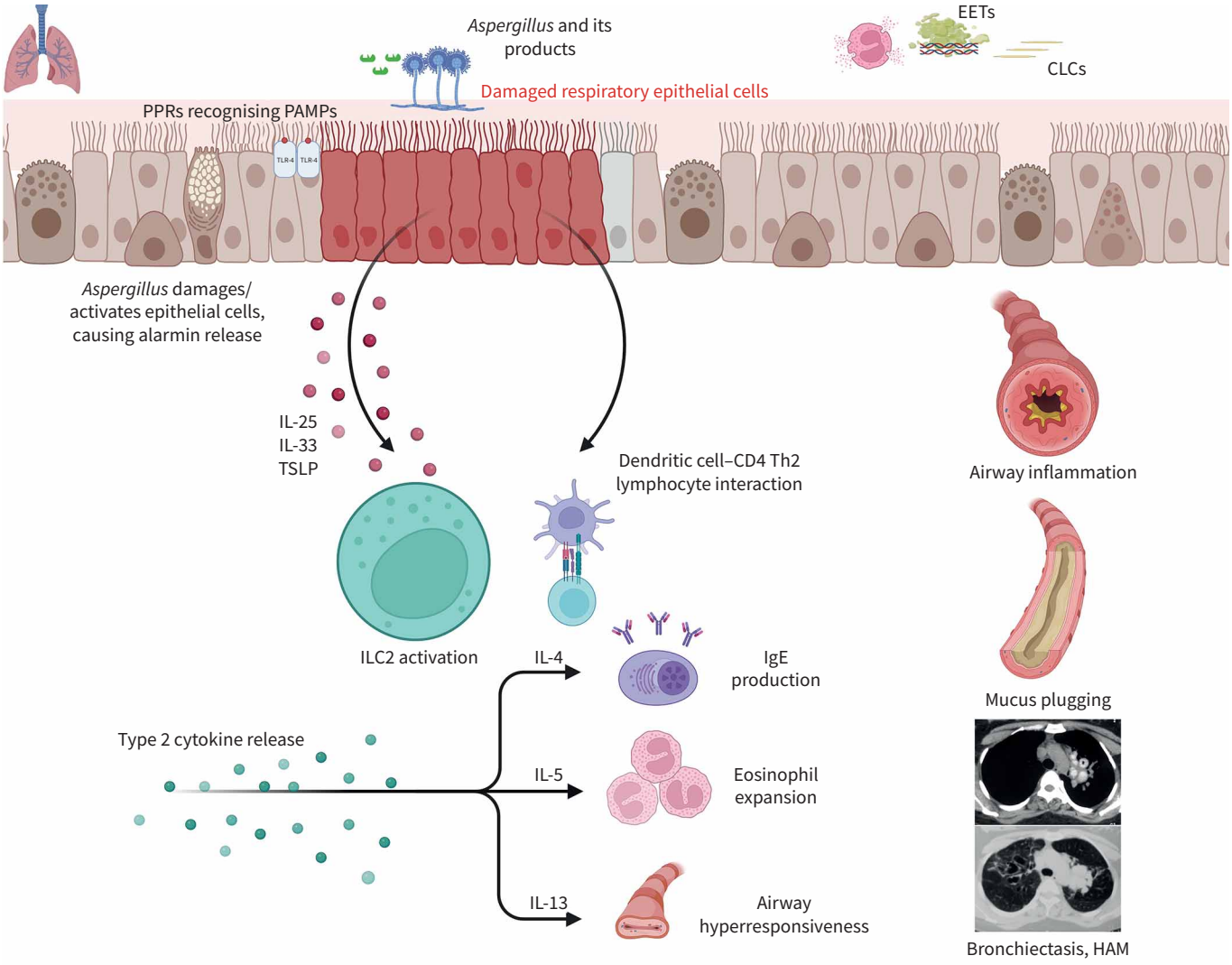

FIGURE 2 The key events in allergic bronchopulmonary aspergillosis (ABPA) pathogenesis include *Aspergillus* colonisation followed by skewed type-2 immune responses. Polymorphisms in airway epithelial receptors and innate and adaptive immune pathways prevent elimination of *A. fumigatus* and promote the development of an aberrant type-2 immune response. Pathogen-associated molecular patterns (PAMPs) from *Aspergillus* (glucan, galactomannan, galactosaminogalactan, proteases) are recognised by pattern recognition receptors (PRRs), including dectin-1 and toll-like receptors (TLRs), at the lung epithelial cell surface. Fungal proteases can damage the respiratory epithelium and result in release of alarmins (interleukin (IL)-33, IL-25 and thymic stromal lymphopoietin (TSLP)), which in turn stimulate the type 2 innate lymphoid cells (ILC2) and $CD4^+$ type 2 lymphocytes. The dendritic cells also recognise fungal proteins and activate allergen-specific type 2 T-cells (Th2 cells). Eosinophils remain the primary mediators of inflammation in ABPA, with the interaction between eosinophils and *A. fumigatus* releasing galectin-10 and forming Charcot–Leyden crystals (CLCs). Subsequently, eosinophils undergo cell death forming histone-rich extracellular traps (EETs) and increase the viscosity of mucus plugs, which contribute to ABPA pathogenesis. The skewed type 2 responses lead to secretion of IL-4, IL-5 and IL-13. IL-4 mediates the class switching and production of IgE antibodies, which attach to mast cells and cause mast cell degranulation on allergen exposure. IL-5 is pivotal for eosinophil recruitment, maturation and survival and is central to eosinophilic inflammation. IL-13 from ILC2 and Th2 cells promotes mucus hypersecretion. Finally, immune activation leads to airway inflammation, mucus plugging and bronchiectasis. HAM: high-attenuation mucus. Figure created with Biorender.com.

[59, 80]. Additional factors contributing to deterioration, notably exacerbations of asthma, COPD and bronchiectasis, all necessitate meticulous exclusion before ABPA-focused interventions are pursued.

Fungal lung disease and mild immunosuppression

Chronic pulmonary aspergillosis (CPA) is an indolent, progressive, debilitating disease caused by *Aspergillus* infection in individuals with pre-existing chronic structural lung disease who may be immunocompetent or have mild immunocompromise interfering with mechanisms of pulmonary fungal

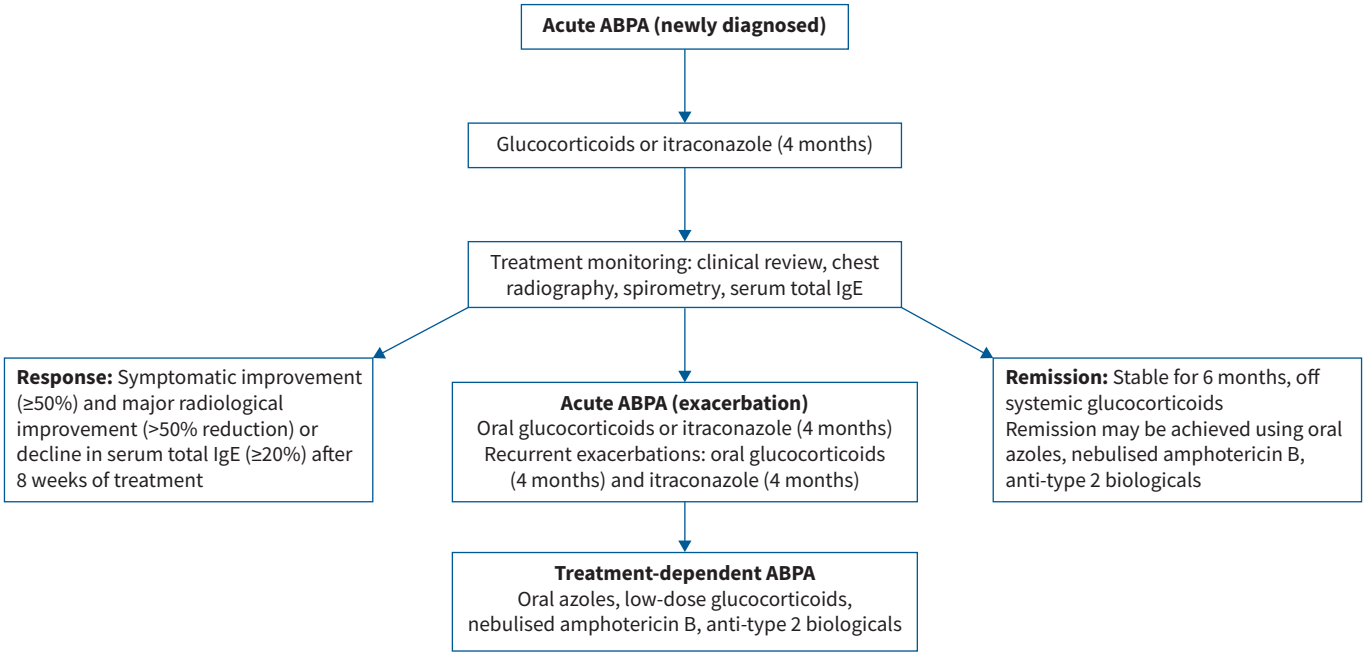

FIGURE 3 Treatment of various allergic bronchopulmonary aspergillosis (ABPA) categories as suggested by the International Society for Human and Animal Mycology-ABPA working group.

clearance [81]. Globally, the most common pulmonary conditions predisposing to CPA are tuberculosis, nontuberculous mycobacterial infection and ABPA, with COPD more common in developed settings [82]. Other prevailing conditions include sarcoidosis, lung cancer and prior thoracic surgery [82–84]. Global epidemiological data are lacking, with an incidence estimated at 22 per 100 000 individuals, which is higher in regions with high tuberculosis prevalence [85]. Presentation is often over months, mimicking deterioration of the underlying chronic lung condition and thus frequently resulting in misdiagnosis. A wide range of radiological phenotypes is seen, from simple aspergillomas (fungal balls) to progressive fibro-cavitary disease, often with overlap [86]. Aspergillomas frequently develop in structurally impaired regions of the lung, such as cavities in individuals with a history of tuberculosis, bronchiectasis and/or sarcoidosis [87–89]. CPA requires a constellation of clinical, radiological, serological and microbiological

TABLE 1 Revised International Society for Human and Animal Mycology ABPA working group consensus criteria for diagnosing ABPA

Predisposing conditions	Asthma, cystic fibrosis, COPD and bronchiectasis
OR	
Compatible clinico-radiological presentation	Expectoration of mucus plugs, finger-in-glove and fleeting opacities on chest radiography, lung collapse and others
Essential components	• *Aspergillus fumigatus*-specific IgE ⩾0.35 kUA·L^{-1}[a] • Serum total IgE ⩾500 IU·mL^{-1}[b]
Other components (any two)	• Positive IgG against *A. fumigatus*[c] • Peripheral blood eosinophil count ⩾500 cells·µL^{-1} (could be historical) • Thin-section chest CT consistent with ABPA (bronchiectasis, mucus plugging and high-attenuation mucus[d]) or fleeting opacities on chest radiography
Important considerations	[a]: a positive type 1 skin test is acceptable when *Aspergillus* IgE is unavailable [b]: serum total IgE <500 IU·mL^{-1} may be acceptable if all other criteria are fulfilled [c]: *A. fumigatus* IgG can be detected using lateral flow assays or enzyme immunoassays; cut-offs for *A. fumigatus* must be developed for specific populations (*e.g.* ⩾27 mgA·L^{-1}, ⩾60 mgA·L^{-1}, ⩾40 mgA·L^{-1} for India, Japan and the UK, respectively) and in the absence of population-specific cut-offs, we suggest using manufacturer recommendations [d]: high-attenuation mucus is pathognomonic of ABPA and confirms ABPA diagnosis even if all other criteria are not fulfilled Elevated IgE against rAsp f1, f2 and f4 can be used as another component

ABPA: allergic bronchopulmonary aspergillosis; Ig: immunoglobulin; CT: computed tomography.

findings [90]. This is challenging, in part due to resource constraints in some regions, but also due to the lack of sensitivity of current diagnostic tests. Although the possibility of co-infection and lung carcinoma should be carefully considered and excluded where possible, due to underlying comorbidity and the risk of lung biopsy, histological confirmation is rarely obtained in clinical practice. The diagnosis often relies on compatible clinical symptoms and radiology alongside a positive quantitative *Aspergillus* IgG or precipitin test [91]. The availability of lateral flow-based *Aspergillus* IgG assays presents a potential low-cost approach for diagnosis in resource-poor settings; however, optimal cut-offs remain unclear, with a significant proportion of CPA demonstrating normal *Aspergillus* IgG due to non-*A. fumigatus* infection or an immunocompromised state [92, 93]. Bronchoscopy to detect *Aspergillus* from lower respiratory tract samples is resource intensive and requires a risk/benefit evaluation, with microbiological culture often showing a poor yield. Use of fungal biomarkers, including galactomannan and *Aspergillus* PCR, requires significant resources and has relatively poor sensitivity [94]. Microbiological confirmation (when possible) is important to identify aetiological species, enable susceptibility testing and exclude co-infection with other pathogens, especially nontuberculous mycobacteria where fungal co-infection is particularly prevalent [95]. In addition, *Aspergillus* species referred to as related or cryptic species (*e.g. A. lentulus*, *A. udagawae*) have a reported prevalence of ∼25% in individuals with CPA in some settings [96]. These are difficult to identify with conventional methods and demonstrate reduced antifungal sensitivity, further highlighting the importance of microbiological confirmation where possible.

Antifungal therapy with first-line azoles (itraconazole, voriconazole) coupled with meticulous therapeutic drug monitoring is advised in cases with demonstrable clinical or radiological advancement rather than simple aspergillomas [97]. The efficacy of a minimum 12-month treatment duration is superior to shorter regimens in averting disease relapse [98]. Adverse effects, however, are common and often require dose adjustment, therapy change or cessation in up to 30%, with high rates of azole resistance after prolonged therapy [99]. Other therapeutic options include newer azole compounds (posaconazole, isavuconazole), intravenous liposomal amphotericin, echinocandins and adjunctive immunotherapy with interferon-γ [100–102]. Surgical resection should be considered in localised or treatment-refractory disease, with good outcomes reported at specialised centres [83]. When surgical intervention is not feasible, percutaneous or bronchoscopic administration of antifungal agents can be considered. Retrospective case series indicate positive outcomes in terms of cavity size reduction, although potential risks including pneumothorax and bronchopleural fistula necessitate thorough expert evaluation and management [103]. Haemoptysis often presents as a life-threatening complication of CPA, with embolisation recommended in massive haemoptysis, and surgery reserved for medically refractory cases or where a lack of interventional facilities or expertise exists [90]. Despite therapy, mortality remains high, with an estimated 5-year mortality of ∼50%, increasing with underlying comorbidities including COPD, nontuberculous mycobacterial infection, low body mass index, antimicrobial resistance and bilateral disease [104]. The current lack of studies and therapeutic trials on CPA underscores the importance of enhancing clinical outcomes through research efforts, particularly within an evolving antifungal trial landscape. These efforts will be improved by use of the recently published EQUAL score for CPA [105].

Invasive fungal lung disease and severe immunosuppression

Invasive fungal pneumonia is classically thought to be a disease of profound immunocompromise, particularly with prolonged neutropenia and lymphopenia. However, there is increasing recognition that invasive fungal pneumonias can affect a much broader population, including patients with more subtle immunocompromise, and therefore are often under-recognised and undertreated. We outline several categories of fungi frequently encountered in critically ill patients: moulds, *Pneumocystis jirovecii* and *Candida*, with a specific focus on invasive pulmonary aspergillosis (IPA), which is associated with particularly high mortality in the severely immunosuppressed.

IPA remains the most common and morbid fungal respiratory infection in immunocompromised patients. Mucorales, *Scedosporium* and *Fusarium* are rarer but can have similar clinical features. Most often, invasive mould infections present as fevers with a consolidation, nodule or mass lesion on imaging [106], but they can also present as tracheobronchitis, especially in lung transplant recipients with vulnerable anastomosis sites [107]. The latter can have normal results on chest imaging with abnormalities only visualised on direct inspection of the airway, which can lead to further complications including stenosis and airway dehiscence [108]. Though locally aggressive, these invasive mould infections typically originate from and remain confined to the respiratory tract, but in the extremely immunocompromised, angio-invasive disease can lead to dissemination to other organs such as the brain, eyes, liver and skin, which leads to a very poor prognosis [109]. A notable exception is *Fusarium*, which disseminates in ∼70% of immunocompromised patients and is frequently associated with positive blood cultures, likely owing to its capacity for *in vivo* sporulation [110].

Demographic studies show an increasing recognition of IPA in the intensive care unit (ICU), beyond patients with the "classic" severely immunosuppressing risk factors of neutropenia, haematological malignancy and prolonged steroid use [111, 112]. Sepsis, one of the most common reasons for ICU admission, leads to a relative state of immune suppression in its later stages, hampering neutrophil function and predisposing to IPA [113–115]. Steroid use, even short courses, can accelerate fungal growth and depress innate immune function [116, 117]. COPD and cirrhosis, both common comorbidities, have been highlighted as conferring intermediate IPA risk, compelling the European Organisation for Research and Treatment of Cancer (EORTC) to revise definitions of invasive fungal infection to include these groups [111, 118].

Viral infection also predisposes to IPA in both immunocompromised and immunocompetent hosts. In epidemiological studies, the prevalence of IPA tracks with viral pandemics [119, 120].

Influenza-associated pulmonary aspergillosis (IAPA) is similarly well established and estimated to affect 19.2% of patients critically ill with influenza [121]. Other respiratory viral infections show similar associations [122, 123]. More recently, COVID-associated pulmonary aspergillosis (CAPA) has been recognised, with a wide variation in reported incidence of 4–35% of critically ill patients, and perhaps even higher rates in the post-vaccination era [124, 125]. However, caution should be used in conflating CAPA and IAPA; CAPA incidence may be overestimated, with more cases diagnosed as "putative" or "probable"; typically has later onset post-ICU admission; and may not contribute to excess mortality in comparison to IAPA [126, 127]. The pathophysiology of post-viral aspergillosis is incompletely understood but is likely multifactorial, with viral-mediated epithelial damage, dysregulated innate and adaptive immunity, suppression of neutrophil-mediated defences and treatment with high-dose steroids and other immunomodulators [128, 129]. Viral–fungal co-infection is not unique to *Aspergillus*, and an association between COVID and invasive pulmonary Mucorales infection has also been noted [130]. Revised EORTC guidelines now include severe viral infections in their list of compatible host factors [118].

Despite expanding "at risk" populations for invasive *Aspergillus* infection, mould growth from respiratory cultures in the ICU is more likely to reflect colonisation than true infection [131], and fungal biomarkers have imperfect sensitivity and specificity, especially in non-neutropenic patients [112, 132]. Radiographic criteria for IPA were developed in neutropenic patients and are often lacking or obscured by other common lung pathology in ICU patients, including acute respiratory distress syndrome, non-fungal pneumonia and/or underlying structural lung disease, making a timely diagnosis of invasive mould infection even more challenging [111].

Pneumocystis jirovecii, a single-celled fungus, nearly exclusively infects immunocompromised hosts and can cause severe, life-threatening pulmonary infection. *Pneumocystis* pneumonia typically presents with diffuse, geographic bilateral infiltrates, though very rarely can be nodular or cavitating, similar to invasive mould infections [133, 134]. Classic groups at risk for *Pneumocystis* include those with poorly controlled HIV, recipients of prolonged high-dose corticosteroids and other individuals with severe impairments in T- and B-cell immunity; knowledge of these risk factors has allowed for guideline-based targeted chemoprophylaxis [135].

The incidence and severity of *Pneumocystis* infections in people without HIV have been rising, and patients previously not considered for chemoprophylaxis are increasingly diagnosed [136]. Increased vigilance for *Pneumocystis* should be practised in patients on immunotherapy (*e.g.* checkpoint inhibitors), tyrosine kinase inhibitors, anti-CD20 inhibitors and newer bispecific antibody agents, though prophylaxis is not yet universally recommended for these groups [137–140]. The increased incidence of *Pneumocystis* in the non-HIV population may be explained in part by the increased use of molecular diagnostics, such as *Pneumocystis*-targeted PCR, broad-range fungal PCR and plasma mNGS, though these modalities also can identify incident colonisation and lead to false positive diagnoses [141, 142]. Traditional *Pneumocystis* diagnostics, including microscopy with silver staining and β-D-glucan, have poorer performance in non-HIV immunocompromised patients due to lower organism burden [143, 144]. Generally, prognosis for *Pneumocystis* is favourable with early appropriate treatment, so a high index of suspicion is critical.

Candida species are perhaps the most isolated fungal organism from critically ill patients. However, their isolation from respiratory tract samples in almost all cases represents colonisation rather than true infection and does not warrant antifungal treatment. *Candida* species are common commensal flora of the oral, respiratory and upper gastrointestinal tracts, and their detection in culture is promoted by the use of broad-spectrum antibiotics, a common practice in ICU patients [145]. In an autopsy study of 135 ICU patients with pathological evidence of pneumonia, more than half had *Candida* growth documented from

respiratory samples, but none had definitive evidence of pulmonary candidiasis [146]. Importantly, a smaller autopsy study, restricted to immunocompromised oncology patients with pneumonia, demonstrated a 14% prevalence of histologically proven pulmonary candidiasis, so this population may be an exception [147]. Additionally, multifocal *Candida* colonisation (respiratory tract, urine, skin) is often associated with higher risks of systemic invasive candidiasis by translocation of yeast from the digestive tract [148]. Despite this, *Candida* isolation from the respiratory tract should not reflexively trigger antifungal treatment.

Endemic mycoses

Endemic mycoses will be briefly discussed outside of this framework, because they infect both immunocompromised and immunocompetent patients with a vast range of severity, from asymptomatic infection to fatal invasive disease. The endemic mycoses (*i.e. Coccidioides*, *Histoplasma*, *Blastomyces*, *Paracoccidioides*, *Sporothrix* and *Talaromyces*) are a diverse group of fungal organisms that have specific ecological niches and are thermally dimorphic with both yeast-like and mould-like states [149]. Depending on the specific organism, infection can be primary or represent reactivation of latent disease, the latter more common in immunocompromised hosts. In both scenarios, dissemination to various sites, including skin, the central nervous system and lymphatics, can occur. Endemic mycoses remain under-recognised causes of community-acquired pneumonia, particularly when they manifest outside of traditional geographic areas [149, 150]. A growing body of work now demonstrates that the historically accepted geographic distributions of individual mycoses is expanding due to several factors, including global climate change, and thus broader clinician awareness is critical in preventing delayed or missed cases that could benefit from antifungal treatment [151, 152]. While still relatively rare compared to the other fungal infections discussed in this review, endemic mycoses can lead to severe and sometimes fatal infections, with a US-based study estimating an in-hospital mortality of 5% in children and 7% in adults, with the majority of infections and deaths in immunocompetent patients [153].

Though technically not an endemic mycosis due to lack of a dimorphic state, *Cryptococcus gattii* is also worth noting given its similar shifting geography. While previously isolated to tropical regions including Australia and Papua New Guinea, in the last few decades the evolution of a different molecular genotype has led to an ongoing outbreak in western Canada and the USA [154–156]. In contrast to *Cryptococcus neoformans*, which has a worldwide distribution and infects immunocompromised individuals, *C. gattii* infections often occur in otherwise healthy hosts, with similar disease manifestations to pneumonia and meningoencephalitis [157, 158].

The pulmonary mycobiome in chronic respiratory disease

mNGS has debunked the dogma of sterile lungs, and we now recognise a diverse resident microbial community, even in health. Like the bacteriome, the mycobiome (the fungal microbiome) in healthy lungs is derived from the oropharynx and upper respiratory tract, largely through micro-aspiration [159, 160]. Owing to the lung architecture and environment, the mycobiome is transient and highly variable, with increasing evidence suggesting key differences between mycobiomes in the healthy state (eubiosis) and those with disease (dysbiosis) (figure 4).

In healthy lungs, the mycobiome is mainly composed of Ascomycota, characterised by *Candida*, *Saccharomyces* and *Cladosporium* species [159, 161–166]. As the healthy lung evolves to one with disease, lung mycobiomes influence microbial co-habitants and modulate the host immune-inflammatory response, contributing to the onset and progression of lung disease [159, 164]. While the role of the mycobiome has been studied in several CRDs, work focused on mycobiomes specifically in fungal lung disease states is lacking. However, important work in SARS-CoV-2 pneumonia is emerging, illustrating reduced fungal diversity and potentially beneficial effects of antifungal treatment at ICU admission in reducing *A. fumigatus*-associated mortality in severe COVID-19 [167–170].

The mycobiome in CRDs is predominantly characterised by the genera *Aspergillus* and *Candida*, while in asthma *Malassezia*, a lipophilic basidiomycetous yeast, exhibits a higher abundance during acute exacerbations and in severe asthma [171–175]. Important differences in fungal (and bacterial) microbiota are correlated to asthma endophenotypes [175]. The role of fungi in COPD is emerging, with two distinct mycobiome signatures described: one associated with *Saccharomyces* and increased symptoms, and another with *Aspergillus*, *Penicillium* and *Curvularia*, frequent exacerbations and higher mortality [3, 18, 165, 176, 177]. *Pneumocystis jirovecii* is over-represented in the lung mycobiome of HIV-positive COPD patients, highlighting its potential role in COPD pathophysiology [176, 178]. Growing evidence in CF suggests that the fungal community has a key role in disease, with even *Candida* associated with lung function decline and progressive disease [8]. *Malassezia* is frequently reported in CF and potentially plays a role in recycling lipids in microbiota, particularly during exacerbations [179–182]. A diversity of moulds

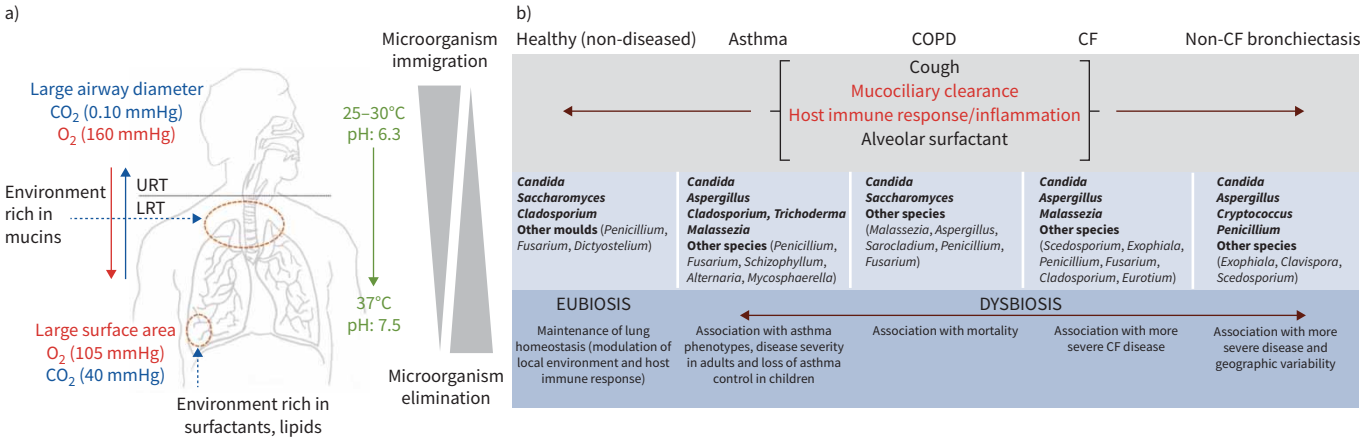

FIGURE 4 A summary of the homeostatic mechanisms to maintain the lung mycobiome in health and its composition and clinical correlates in chronic respiratory disease. a) Bidirectional flux from the oropharyngeal area, or upper respiratory tract (URT), to the lower respiratory tract (LRT) with biotic (bronchial epithelial cells, respiratory cilia, diameter and cell surface exchanges) and abiotic (temperature, pH, O_2/CO_2 pressures, airway mucus rich in mucins, a lipid-rich surfactant) factors maintaining a relatively low airway fungal biomass (the mycobiome). The mycobiome maintains a dynamic balance between fungal immigration, driven by inhalation, salivary micro-aspiration and mucosal dispersion, and elimination, driven by cough, mucociliary clearance, innate and adaptive host immune response and antimicrobial activity of alveolar surfactant. This constant dynamic of flux ensures the mycobiome is transient and mobile, with intimate links to the external environment. In health, the lung mycobiome is in a eubiotic state. b) By contrast, dysbiosis of the lung mycobiome occurs across several chronic respiratory diseases including asthma, COPD, cystic fibrosis (CF) and non-CF bronchiectasis. Mechanisms of microbial clearance are differentially impaired based on the pathophysiology of the underlying disease and indicated as normal (black text) to abnormal (red text). In diseased lungs, the mycobiome is more long-lasting and exhibits change, contributing to disease progression.

is also observed; they are generally considered transient colonisers, except for *A. fumigatus*, *Scedosporium apiospermum* and *Exophiala dermatitidis*, given their multiple and sequential detections [179, 181–184]. Pulmonary exacerbations in CF are associated with an "Attack" community composed of virulent bacteria and viruses [181, 185–189]. *Malassezia* and *Aspergillus* form part of this community [182]. According to the "Climax-Attack model", the "Attack" community is transient, followed by stability characterised by a "Climax" community [185]. The "Climax" community includes bacteria such as *Pseudomonas aeruginosa* and the fungus *Scedosporium*, which is associated with poor lung function [182, 188]. *Aspergillus*, *Candida* and *Penicillium* represent the dominant genera in the non-CF bronchiectasis lung, with *A. fumigatus*, *E. dermatitidis* and *S. apiospermum* the most frequently detected species [183]. In association with *Cryptococcus* and *Clavispora*, *Aspergillus* is linked with progressive bronchiectasis, with specific dominant *Aspergillus* species dependent on the patient's geographic origin [32]. An integrative microbiomics approach incorporating multi-kingdom analysis demonstrated that *Cryptococcus* is associated with exacerbation risks in bronchiectasis [190].

Fungal signatures as treatable traits in chronic respiratory disease

While fungal colonisation is commonly observed in CRDs, it is unclear when and how such fungi serve as bystanders or pathogens, and to what extent and under what circumstances they contribute to disease onset and progression. Studies evaluating the clinical consequences of fungal colonisation in CRDs reveal contrasting results in relation to symptoms, lung function and exacerbations (table 2) [8, 11–16, 28]. Furthermore, evidence of fungal eradication has proved inconclusive in CF [13, 28, 29]. Nonetheless, emerging evidence demonstrates clear associations between *Aspergillus* colonisation and the clinical spectrum of aspergillosis, ranging from sensitisation to invasive disease, proposing a role for fungal colonisation as a precursor to the development of fungal lung disease in susceptible individuals [131, 215–220]. Further studies are necessary to elucidate mechanisms related to *Aspergillus* colonisation in various CRDs. Whether fungal signatures as we currently understand them represent a treatable trait in CRD also remains to be determined.

Fungal sensitisation and ABPM/ABPA are associated with adverse outcomes in patients with CRDs (table 2) [30, 191, 196–198, 205–207, 221]. SAFS and ABPA in asthma link to small airway dysfunction, exacerbations, life-threatening asthma and high corticosteroid burden [30, 191, 196–198, 205, 221]. Likewise, in CF, sensitisation to *Aspergillus* is associated with poorer lung function and exacerbations, detectable using basophil surface biomarkers [22, 193–195]. Reduced serum vitamin D levels are associated with Th2 inflammatory

TABLE 2 Fungal signatures in chronic lung disease and associated clinical outcomes with potential treatment approaches

Fungal signature	Disease	Outcomes	Potential treatment
Colonisation	CF	↑ Radiological abnormalities [11] No difference in lung function [11–13] ↓ Lung function [8, 16] ↑ Exacerbations [8, 14, 15]	Antifungals [192]
	Asthma	*Aspergillus* sensitisation ↓ Lung function [31] Neutrophilic inflammation [30] ↑ Exacerbations [191]	
	COPD	Progression to aspergillosis [19] ↑ Exacerbations [17, 18] Prolonged hospital stay [7]	
	Bronchiectasis	↑ Exacerbations [32, 33]	
Sensitisation	CF	↓ Lung function [22, 193–195] ↑ Exacerbations [22, 193]	Corticosteroids [69, 71] Antifungals [192, 201–204]
	Asthma	↓ Lung function [30, 191, 196] ↑ Exacerbations [197, 198]	
	COPD	↓ Lung function [5, 49] ↑ Exacerbations [49, 199]	
	Bronchiectasis	↓ Lung function [200] ↑ Disease severity [200]	
ABPA	CF	↓ Lung function [195]	Corticosteroids [69, 71]
	Asthma	↓ Lung function [205] ↑ Exacerbations [205]	Antifungals [201, 203, 208] Biologicals [209–214]
	COPD	↑ Mortality [206] ↑ BCO [55]	
	Bronchiectasis	↓ Lung function [205, 207] ↑ Exacerbations [207]	

CF: cystic fibrosis, ABPA: allergic bronchopulmonary aspergillosis; BCO: bronchiectasis–COPD overlap.

responses in CF-ABPA; however, treatment with vitamin D in clinical trials conferred no demonstrable clinical, radiological or immunological improvement [222, 223]. Case series and small retrospective studies assessing biological therapies in CF-ABPA show favourable results, and while still lacking prospective evaluation in CF, fungal sensitisation and ABPA are clearly important treatable traits in asthma and CF [209–214].

The role of fungi as a treatable trait is less recognised in COPD and bronchiectasis, although the high prevalence of fungal sensitisation is reported in both conditions. Environmental exposure represents a key risk for the development of fungal sensitisation, with measurable responses detectable to outdoor and indoor air fungi and associated allergens in COPD [199]. While ABPA is an established cause and consequence in bronchiectasis but infrequent in COPD, it is associated with increased systemic inflammation and higher mortality compared to non-COPD settings [206]. In contrast to asthma, evidence for biological therapy in COPD and bronchiectasis is only starting to emerge. Considering the vast patient heterogeneity existing in these disease states, personalised endophenotyping will likely be required to identify patient groups that would significantly benefit from leveraging fungal signatures as treatable traits [224, 225].

Molecular diagnostics in fungal lung disease

The inherent limitations of fungal culture and immune-based approaches relying on fungal antigens and/or antibodies necessitates fresh molecular diagnostics to better identify fungal lung disease [226]. Galactomannan detection in serum and BALF remains valuable for the early detection of invasive aspergillosis, particularly in immunocompetent individuals; however, it suffers from poor sensitivity [227–229]. While molecular approaches can confirm culture results, using PCR, digital PCR and mNGS directly on primary clinical specimens, including sputum, BALF and blood, offers significantly improved diagnostic sensitivity, specificity and timeliness against a wide range of fungal pathogens to the species level [230]. Multiplex approaches combine pathogen identification with antifungal resistance testing; for instance, identifying azole (*i.e.* mutations in *CYP51A* or *ERG11*) or echinocandin (mutations in *FKS*) resistance by PCR leads to earlier initiation of effective antifungals, likely improving clinical outcome [231]. mNGS

also offers an added advantage of identifying novel fungal pathogens, especially when clinical presentation and/or epidemiology may be suggestive of a fungal infection but not typical for any particular fungal pathogen precluding PCR diagnostics [231, 232].

Molecular diagnostics offer point of care testing, facilitating rapid diagnosis, particularly in low- and middle-income countries, where access to centralised laboratories is limited [233]. Commercially available and clinically validated PCR assays are widely used to diagnose aspergillosis with BALF or blood [234, 235], candidiasis using blood [236] and *Pneumocystis* pneumonia using BALF [237, 238], with relatively high accuracy and a rapid turnaround time [239]. The specificity of blood PCR for invasive aspergillosis may be improved with repeat testing, especially in high-risk populations [234]. PCR can also be employed to diagnose some Mucorales species and *Cryptococcus neoformans* [231].

A diverse range of fungal taxa can be detected by mNGS, including *P. jirovecii*, *Aspergillus* and *Candida* species as well as *Cryptococcus*, *Rhizopus*, *Fusarium* and *Alternaria* species, *Talaromyces marneffei* and *Histoplasma capsulatum* [240]. Compared to traditional diagnostic approaches, NGS is highly sensitive and specific and outperforms traditional culture in detecting fungal pathogens, exemplified by the identification of *P. jirovecii*, which is not culturable, and other fastidious fungi such as *Mucor* species [226, 241].

Of note, there are important technical challenges to the use of molecular diagnostics in fungal disease, mostly related to small amounts of fungal DNA often present in clinical specimens [242]. Validation of molecular testing against current gold standards is complicated by the rare nature of some fungal infections. Distinguishing between infection, colonisation and contamination is a challenge with molecular testing [231, 243]. While highly useful in immunocompromised patients with suspected invasive fungal infections, the diagnostic yield of molecular methods is not as high in patients with chronic lung disease who are not necessarily immunocompromised, where a molecular test might be indicative of colonisation and not necessarily invasive infection. This is particularly true in patients with COPD with positive *Pneumocystis* BALF PCR results or even lung transplant recipients with positive *Aspergillus* BALF PCR results. Combining *Pneumocystis* PCR with serum β-D-glucan or *Aspergillus* PCR with galactomannan will significantly increase the specificity of the test [243, 244]. mNGS at present is more cost and resource intensive than culture and PCR, and may require substantial technical and bioinformatic expertise, currently limiting widespread availability [240]. Additionally, fungal genomic data are not widely available, and inadequately curated databases limit NGS detection accuracy [240]. Moreover, overdiagnosis and erroneous association of pathogens with disease can lead to unnecessary treatment [241]. Despite limitations, molecular diagnostics for fungal infection have become an increasingly common diagnostic approach, with significant potential to replace culture [242]. Its potential to improve patient outcomes makes it an attractive and increasingly important approach for the accurate and timely diagnosis of fungal lung infection.

The antifungal drug development pipeline

With the increasing issue of antifungal resistance, a robust antifungal drug development pipeline is imperative. Aerosolisation presents a promising avenue for drug delivery because it delivers a higher drug concentration to the site of infection while avoiding systemic toxicity, reducing adverse events and administration frequency [245, 246]. Several inhaled antifungals have been examined for the treatment of allergic and invasive pulmonary mycoses with varying degree of success and 50–65% cure rates [247, 248]. Amphotericin B is the most widely studied and used, followed by voriconazole and itraconazole. Inhaled amphotericin B has been also used in combination with systemic azole in highly immunocompromised patients [249]. Newer formulations of azoles (PC945 and PC1244) have been developed specifically for inhaled application with promising results, but lack the clinical and outcome data to support their use [249]. In theory, the advantage of inhaled therapy is in limiting systemic side effects and maximising antimicrobial efficacy at the site of the infection. Combining antifungal agents of different mechanisms of action might be beneficial, and is often used. However, data to support this practice remain scarce. A randomised controlled trial comparing voriconazole and anidulafungin to voriconazole monotherapy showed improved survival in a subgroup of patients but, importantly, not the whole cohort [250].

Rezafungin is an echinocandin, targeting β1,3-D-glucan, like caspofungin, micafungin and anidulafungin. The pharmacological modifications incorporated into rezafungin are designed to provide a longer half-life (133 h), permitting less frequent administration [251]. Equivalent efficacy to other echinocandins was demonstrated by the SENTRY 2015 surveillance programme [252]. Similarly, equivalent efficacy to anidulafungin is reported against *Candida* species, with potency against fluconazole-resistant isolates but not all anidulafungin-resistant isolates; hence, its value is in its longer half-life rather than increased spectrum of activity over existing echinocandins [253]. Two pivotal preregistration studies for rezafungin

established clinical efficacy: the ReSTORE trial [254] and STRIVE [255]. These showed equivalent microbiological cure and mortality outcomes between rezafungin and caspofungin [256].

Ibrexafungerp, a novel synthetic derivative of enfumafungin targeting β1,3-D-glucan synthase, has the added advantage over echinocandins of oral bioavailability [257]. Initial murine studies of candidiasis followed by *in vitro* data from clinical isolates and other animal models show promise [257–259]. However, like echinocandins, ibrexafungerp remains poorly active against Mucorales and *Fusarium* [260]. An open-label phase 2 study assessed the efficacy of ibrexafungerp in 27 patients with invasive candidiasis, with comparison to fluconazole or micafungin as standard of care [261]. Clinical success rates were comparable across all groups with no safety concerns. These clinical findings are consistent with *in vitro* data suggesting ibrexafungerp is fungistatic against *A. fumigatus*, with demonstrable synergy with azoles and amphotericin B against *Aspergillus* species [262]. Further trial data for ibrexafungerp are awaited: the SCYNERGIA trial, which investigated its use in combination with voriconazole compared to voriconazole alone in patients with IPA (ClinicalTrials.gov: NCT03672292) has been terminated, while the MARIO study, where an echinocandin followed by either ibrexafungerp or voriconazole was being used to treat patients with invasive candidiasis (ClinicalTrials.gov: NCT05178862), is currently suspended due to manufacturing issues.

Fosmanogepix is a novel first-in-class antifungal targeting Gwt1, an early enzyme in the synthesis of glycosylphosphatidylinositol [263, 264]. Murine neutropenic models suggest it is an effective treatment option for invasive infections with *Scedosporium* and *Fusarium* [265] and *Candida* [266], and promising for *Rhizopus arrhizus* [267]. A small phase 2 study for invasive candidaemia showed a 30-day survival of 89% [268] with a second phase 2 trial a success rate of 80% [269]. Results of an open-label trial in patients with *Aspergillus* or rare moulds (ClinicalTrials.gov: NCT04240886) showed a 43% mortality rate (nine out of 21) with early study termination by the sponsor to concentrate on phase 3 studies.

Olorofim (F901318) represents a further novel antifungal inhibiting the enzyme dihydroorotate, a key step in pyrimidine synthesis [270]. *In vitro*, it is highly active against azole-resistant *A. fumigatus*, *Scedosporium* and *Fusarium* species and endemic mycoses but shows no activity against Mucorales or *Candida* [271–275]. Provisional results of a phase 2b open-label study in 100 patients with invasive mould infections reported a 44% and 39% success rate at days 42 and 84, respectively [276]. In 2023, the US Food and Drug Administration declined approval, citing a need for more clinical data. A phase 3 study in invasive aspergillosis (ClinicalTrials.gov: NCT05101187) is underway while a phase 2b study in patients with invasive fungal disease lacking other therapeutic options has been recently completed (ClinicalTrials.gov: NCT03583164).

Finally, several other agents remain in the pipeline: tetrazoles (VT-1161, VT-1129 and VT-1598), novel azoles with lower affinity for human cytochrome P450 isoenzymes (CYP2C9, CYP2C19 and CYP3A4) resulting in lower potential for drug–drug interactions, are promising with activity against some fluconazole-resistant isolates such as *Candida glabrata*, *C. krusei* and *C. auris* [277]. T-2307 is an arylamidine similar to pentamidine targeting fungal mitochondria with activity against most *Candida*, *Cryptococcus neoformans*, *C. gattii* and *A. fumigatus* [266, 277–283]. Further trials are awaited.

In well-selected patients with invasive fungal infections for which medical therapy fails, surgical resection using wedge resection or lobectomy might offer an alternative option with acceptable outcomes [284, 285].

Conclusions

Fungal lung disease remains a rising global health concern with increasing burden. Recognition is difficult and management challenging due to the diverse spectrum of clinical presentations, broad range of fungal pathogens and increasing antifungal drug resistance. Significant progress is being made in understanding its pathophysiology, the spectrum of illness and the key interplay between the host immune system and mycobiome. Novel diagnostics will improve our recognition and the drug development pipeline our treatment options. Harnessing molecular approaches including “omic” technologies and strengthening collaborations between academic, clinical and industry partners is imperative to make progress toward more personalised diagnosis and treatment across the spectrum of fungal lung disease. Standardised guidelines for recognition, diagnosis and management must be implemented and regularly updated in parallel with research advances to maximise the effect at the individual patient level.

Acknowledgements: The authors would like to acknowledge the Academic Respiratory Initiative for Pulmonary Health (TARIPH) and the Lee Kong Chian School of Medicine Centre for Microbiome Medicine for collaborative support.

Author contributions: T.K. Jaggi, R. Agarwal, P.Y. Tiew, A. Shah, E.C. Lydon, C.A. Hage, G.W. Waterer, C.R. Langelier and L. Delhaes contributed to study design, data collection, interpretation and writing of the final manuscript. S.H. Chotirmall contributed to study design and conception, data collection, interpretation and analysis, writing of the final manuscript, and obtained study funding.

Conflict of interest: S.H. Chotirmall has served on advisory boards for CSL Behring, Pneumagen Ltd and Boehringer Ingelheim, on data safety monitoring boards for Inovio Pharmaceuticals and Imam Abdulrahman Bin Faisal University, and has received personal fees from AstraZeneca and Chiesi Farmaceutici, all unrelated to this work. The remaining authors have no potential conflicts of interest to disclose.

Support statement: This work is supported by the National Research Foundation Singapore under its Open Fund-Large Collaborative Grant (MOH-001636) and administered by the Singapore Ministry of Health's National Medical Research Council (S.H. Chotirmall); the Singapore Ministry of Health's National Medical Research Council under its Clinician-Scientist Individual Research Grant (MOH-001356) (S.H. Chotirmall); Clinician Scientist Award (MOH-000710) (S.H. Chotirmall); Transition Award (MOH-001275-00) (P.Y. Tiew); Open Fund Individual Research Grant (MOH-000955) (S.H. Chotirmall); and the Singapore Ministry of Education under its AcRF Tier 1 Grant (RT1/22) (S.H. Chotirmall). Funding information for this article has been deposited with the Crossref Funder Registry.

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