Review Article



# Invasive and chronic fungal lung infections

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**Abstract:** Fungi are increasingly recognized as a cause of respiratory infection, particularly affecting individuals with either immune deficiency or localised lung destruction. The normal human host response effectively controls airborne fungi, but specific polymorphisms are associated with increased risk of developing fungal lung infection. Invasive fungal disease (IFD) is associated with neutropenia and haematological stem cell transplants. They are difficult to diagnose with certainty though the use of cross-sectional imaging and biomarkers has allowed targeted patient treatment. Mortality rates, though improving with antifungal therapy, remain unacceptably high. Chronic pulmonary fungal disease is associated with chronic respiratory disorders and is also difficult to diagnose with certainty. Treatment is chronic and often poorly tolerated, and even when successful unable to reverse existing lung damage. Further research is required to improve both diagnostics and therapy to improve outcomes in these infectious diseases.

**Keywords:** Respiratory infection; fungal infection; invasive aspergillosis; chronic pulmonary aspergillosis (CPA)

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## Background

Fungi increasingly contribute to respiratory symptoms, causing a variety of clinical phenotypes such as invasive fungal disease (IFD) in the severely immunocompromised, chronic pulmonary disease in patients with local immune defects, allergic phenomena such as severe asthma with fungal sensitisation (SAFS) and allergic bronchopulmonary aspergillosis (ABPA). Treatment can be difficult and the antifungals currently in use can have significant side effect profiles. As such they can prove problematic for the general physician. Herein we review two clinical syndromes of invasive fungal lung infection and chronic fungal lung infection with readers directed to a recent excellent review regarding the allergic disorders (1).

Fungi are eukaryotic organisms, with a true nucleus and organelles. Their cell membranes contain ergosterol and are encased by a rigid cell wall composed of chitin, β-glucans, and mannans. They obtain nutrients by secreting hydrolytic enzymes that digest complex polymers, absorbing the resulting products. Fungi do not form complex organs, and exist either as single cells or a chain of cells (hyphae). Moulds are multicellular fungi that exist in the vegetative state as a mass of branching hyphae (mycelium), which have rigid cell walls, containing septae, and grow at the apex. Yeasts are single cells that propagate by budding, which may result in individual daughter cells, or a chain of attached cells. Some species can change their growth form during tissue invasion in humans, these are termed dimorphic. Fungi reproduce by sporulation, often asexual replicas of the parent cell (conidia), but others are capable of sexual reproduction, for example with the production of fruiting bodies such as mushrooms.

Fungal conidia are part of the airborne flora (2). Some conidia are the perfect size to be inhaled (e.g., Aspergillus species at 2–3 μm) and penetrate to terminal bronchi and

**Table 1** Single nucleotide polymorphisms (SNP) associated with Aspergillus infections

| Gene | SNP effect | Disease | Reference |
|---|---|---|---|
| CXCL10 | Reduced production from dendritic cells | Invasive aspergillosis (IA) | (5) |
| DECTIN1 | Decreased surface expression, and binding capacity | IA | (6) |
| IFNG | Increased levels | Chronic pulmonary aspergillosis (CPA) | (7) |
| IL1RN, IL1A, IL1B | Increased CRP | IA | (8) |
| IL10 | Reduced levels | CPA | (7) |
| IL15 | Increased levels | CPA | (7) |
| Il23R | Reduced IL17 | IA | (9) |
| MASP2 | Impaired MBL function | IA | (10) |
| MBL2 | Reduced levels or impaired activity of MBL | IA, CPA | (10) |
| TGFβ | Decreased TGFβ | CPA | (7) |
| TLR1 | Unclear | IA | (11) |
| TLR4 | Unclear | IA, CPA | (12) |
| TLR6 | Unclear | IA | (11) |
| TNF | Decreased TNF | CCPA | (7) |
| TNFR1 | Decreased TNFR1 mRNA | IA | (13) |

CRP, C reactive protein; MBL, mannose binding lectin; TGFβ, transforming growth factor β; TNF, Tumour necrosis factor.

alveoli (3), their ubiquitous nature (they are present in soils, water, dust, and in particular in decaying vegetation) ensure that we all breathe in some fungal spores on a daily basis. If not dealt with, they germinate into hyphae and secrete proteolytic enzymes which cause tissue damage, allowing tissue invasion. This results in parenchymal lung damage, angioinvasion, thrombosis, infarction and haematogenous dissemination. However they rarely cause disease, as unless the local immune system is deficient in some way, conidia are dealt with rapidly.

Initial barriers to disease are the mucociliary barrier, which involves physical clearing by cilia moving the mucous layer (4) and soluble proteins within the mucus with immune properties such as defensins, lysozyme, and secretory IgA. Once entering the alveolus, host defense is largely dependent on the presence and effectiveness of alveolar macrophages. These immune sentinels express cell surface pattern recognitions receptors (see *Table 1*), some of which recognize and bind fungal pathogen associated molecular patterns (PAMP). Dectin-1, a C-type lectin, binds β-glucan in the fungal cell wall, and induces phagocytosis as well as macrophage activation and consequent chemokine and inflammatory cytokine release. Toll like receptor (TLR) signalling molecules (TLR2, 4, 9) recognize a variety of fungal PAMPs such as zymosan, phospholipomannan, and fungal DNA.

The chemokine and inflammatory response induces the migration of neutrophils to the local alveolar environment. This vastly increases the phagocytic capacity of the local immune system, allowing fungal uptake and killing mediated by reactive oxygen species. Neutrophils are also capable of creating neutrophil extracellular traps that allow the killing of hyphae too large to engulf. The adaptive immune response also plays a role in fungal clearance. A dominant Th1 response, resulting in IFNγ secretion and opsonizing antibodies, increases phagocyte activity, and promotes fungal clearance. Conversely, a Th2 response promotes fungal allergic reactions, and Th17 mediated mucosal immunity is important in protection against mucocutaneous candidiasis.

## IFD

Immunocompromised patients are at high risk of developing IFD, particularly patients with haematological malignancies, after haematopoietic stem cell transplants,

**Table 2** EORTC criteria for the diagnosis of invasive fungal disease

| Category | | Criteria |
|---|---|---|
| Possible | A) | Risk factors (neutropenia >10 days, allogeneic stem cell transplant, prednisolone 0.3 mg/kg for ≥3 weeks, T cell immunosuppressant, inherited severe immunodeficiency) |
| | B) | CT signs (nodule +/– halo, air-crescent sign, cavity) |
| Probable (one from A, B & C) | A) | Risk factors (neutropenia >10 days, allogeneic stem cell transplant, prednisolone 0.3 mg/kg for ≥3 weeks, T cell immunosuppressant, inherited severe immunodeficiency) |
| | B) | CT signs (nodule +/– halo, air-crescent sign, cavity) |
| | C) | culture in bronchoalveolar lavage fluid (BALF) or sputum, +ve galactomannan in BALF or serum, or +ve β-d-glucan in serum |
| Definite | | Culture of fungus from normally sterile sites (not BALF), or the demonstration of tissue invasion on biopsy |

and recipients of solid organ transplants. Up to 30% of patients not on antifungal prophylaxis develop a fever of unknown origin (FUO) when neutropenic, however the majority will have bacterial infections. Symptoms are non-specific and include dyspnoea, cough, pleuritic chest pain, and haemoptysis. Aspergillus species (most commonly *A. fumigatus*, but also *A. flavus*, *A. terreus*, *A. nidulans* and *A. niger*) account for the majority of pulmonary IFD (14), though other species such as Mucorales, and Fusarium have become more common (15). *Pneumocystis jirovecii* also causes respiratory infections in the immunocompromised but does not respond to antifungals, and is not considered further here. The endemic mycoses (*Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis* etc.) cause infections in the immunocompetent in defined geographical areas, and are not considered further here.

The 'European Organization for Research and Treatment of Cancer' (EORTC) has set out international consensus criteria for IFD (16) (*Table 2*). While these criteria were initially developed to guide inclusion into trials they provide a useful starting point to guide treatment with antifungals.

While microbiological culture is ideal, the sensitivity of microscopy and culture from bronchoalveolar lavage fluid (BALF) is no higher than 50% (17,18). Culture has the added value of allowing *in vitro* drug susceptibility testing, particularly with the increase in incidence of azole resistant Aspergillus isolates, though breakpoints are as yet not standardised. Notably the case fatality of patients with resistant Aspergillus is higher than non-resistant isolates (19).

Fungal cell wall components such as galactomannan (GM) and β-d-glucan (BDG) are now widely used to increase diagnostic sensitivity. GM is found in Aspergillus cell walls, so is particularly useful in the diagnosis of invasive aspergillosis (IA), with a serum GM of optical density (OD) <0.5 having a sensitivity of 41-78% and specificity of 60–95% (20), giving a 95% negative predictive value for IA (21,22). A single sample OD ≥1 or 2 separate serum samples OD ≥0.5 is considered positive by the FDA (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM420236.pdf). OD is measured at 450nm, with OD expressed a ratio of sample compared to a 'cut off' control, with negative and positive controls establishing a valid test. Semi-synthetic β-lactams can cause false positive results up to 5 days after discontinuing them, as can cotton swabs, severe mucositis, severe gastrointestinal graft versus host disease, IgG myeloma and flavoured frozen desserts containing sodium gluconate. The use of mould active antifungals can cause false negative results (23), particularly in the context of surveillance (24). BALF levels of GM have good predictive value, both in haematological (21,25) and non-haematological patients (26), with a sensitivity of 87% and specificity of 89% using a cut off of ≥0.5, though many use a single sample (2 aliquots) cut off of ≥1 as positive (20). The data for serum GM in non-haematological patients is less good, with better results in BALF. A BALF GM of ≥0.5 was associated with >90% specificity in solid organ transplants, and specificity of 100% with a cut off of ≥1. Similarly in critical care patients, BAL GM ≥1 gives sensitivity of 100% and specificity of 89% (20).

BDG is expressed in most fungal cell walls (excluding Mucorales and Cryptococci), and can be used as a serum marker for both yeasts and moulds, though false positive results can be seen in with some Gram positive organisms, and the concomitant use of immunoglobulins

 

or some dialysis membranes (27). This gives it an overall sensitivity of 77% and specificity of 85% (28) with a cut off of 80 pg/mL (intermediate 60–79 pg/mL). Aspergillus polymerase chain reaction (PCR) appears promising with high sensitivity in blood and BALF (29-31) but lack of standardization across laboratories has precluded its incorporation into recent IDSA diagnostic guidelines. A lateral flow device has been developed that gives point of care information on the presence of fungal cell wall constituents in respiratory samples, with sensitivity and specificity approaching that of PCR, with reported BALF sensitivities of 80-10% and specificity of 81–95% (20,32,33).

While conventional chest X-ray has low sensitivity for diagnosing IFD, the presence of nodules, ground glass halos, cavities and air crescent signs (34,35) can be seen in IA. Early cross sectional CT has been associated with earlier diagnosis (36) and is now standard of care when investigating unresolving fever in the immunocompromised patient.

As untreated pulmonary IFD has a high mortality rate [86%, (37,38)], there has been a move towards antifungal prophylaxis and early treatment of possible IFD. However, as antifungal drugs are costly and can cause significant toxic adverse events, there has been a drive towards stratifying patients using radiology, GM, and PCR prior to treatment with antifungals (39,40). The addition of biomarkers in the decision to commence antifungals significantly reduced antifungal use in a 'real world' Australian study (41). A recent meta-analysis comparing empirical antifungal therapy with diagnostic test-guided pre-emptive antifungal therapy, showed that a pre-emptive approach significantly reduced the use of antifungals (42) without affecting mortality. A cost analysis showed equipoise between the two groups, though slightly favouring the pre-emptive approach. This varied due to the cost of the drug used in the studies reviewed. However, as mortality rates are high, empirical antifungals are recommended in at risk patients who are persistently febrile despite broad-spectrum antibiotics whilst investigations are pending. There is no evidence of superior outcome if treatment was commenced on the day of fever, rather than after 4 days of broad spectrum antibiotics (43). This is because bacterial infections remain the commonest cause of fever in the neutropenic patient.

First line treatment of neutropenic patients with IA is with intravenous voriconazole (21) or liposomal Amphotericin B (44-46). A recent trial showed that isavuconazole was non-inferior to voriconazole with a marginally better adverse event profile (47). Posaconazole has not been trialled for primary IA, but salvage studies suggests it is effective for refractive IA (48). There is evidence that monitoring of therapeutic drug levels can help ensure therapeutic doses of azoles in blood (49), and improve outcome (48,50,51). The echinocandins have been approved for second line use, as they reduce mortality compared to placebo, though the mortality rates appear to be higher that with voriconazole (albeit without head to head trials) (52-54).

Combination therapy with two antifungals has been used for salvage therapy (55-57) though there are varied results from using combination therapy as first line therapy: with additional anidulafungin improving mortality rates (though not quite reaching statistical significance) compared to voriconazole alone (58), but the addition of caspofungin having no beneficial effect over voriconazole in another (59). Arguments have been advanced to use dual therapy upfront in the sickest patients. While there are theoretical reasons that azoles and polyenes may have antagonistic effects, this has not been borne out in clinical trials (60). Although there are little data on the treatment of breakthrough IA (i.e., with the use of prophylactic posaconazole), if therapeutic levels had been achieved, it seems sensible to recommend a class switch, usually to liposomal amphotericin.

Often treatment is blind, and rarely with information such as antifungal susceptibility patterns. GM correlates with fungal burden, and has been used to monitor response to treatment, and decay in levels are associated with successful outcome (61-63), with a >35% reduction in serum GM after 1 week associated with successful clinical outcome. Re-imaging after commencing treatments should not take place before 2 weeks, as there can be a temporary increase in the size of pulmonary lesions, in particular with neutrophil reconstitution (35). Usually antifungals are carried on for 6 to 12 weeks depending on clinical response, as many of the therapeutic trials have used 12 weeks survival as an endpoint, though there are little available data to support this duration of treatment.

Fusariosis, due to the Fusarium genera (most commonly *F. solani* and *F. oxysporum*) is second to IA as a cause of invasive mould disease and associated with prolonged neutropenia. *In vitro* testing suggests reduced susceptibility to the current range of antifungals, often seen in the context of breakthrough of patients on echinocandins or azoles (64-66). Compared to other IFD, there is an increase in rates of fungaemia and serum GM levels >0.5 have a sensitivity of up to 83% and specificity of 67% (67,68). Currently voriconazole, posaconazole and liposomal

 

amphotericin are thought to be effective in fusariosis, though described survival rates at 12 weeks are only 33% to 42% (69,70) .

Mucormycosis, invasive mucormycete infection [commonly *Rhizopus* and *Lichtheimia* genera (71)], is difficult to differentiate from IA on clinical, radiological, and microbiological grounds and causes approximately 1.5% of IFD (72). Notably they have little GM in their cell wall, rendering this test ineffective. However the reverse halo sign is noted in early disease and targeted 18s PCR can be used to speed up diagnosis. They are constitutionally resistant to voriconazole, and treatment requires liposomal amphotericin, posaconazole or isavuconazole (+/– echinocandin). Mortality remains high (38–43% at 12 weeks) despite treatment (73,74). They have become responsible for healthcare associated outbreaks (75) with haematological malignancy and diabetes mellitus being particular risk factors.

## Chronic pulmonary aspergillosis (CPA)

CPA is estimated to have a worldwide prevalence of 2.2 million people (76-78) and presents with non-specific symptoms such as cough, haemoptysis, fever, dyspnoea and weight loss. In particular it develops as a complication of lung damage due to tuberculosis, chronic obstructive pulmonary disease (COPD), ABPA, and sarcoid (79,80).

A 20 year retrospective analysis of 387 patients referred to a national centre showed a 5 year survival of 62%, with 98% patients on antifungal therapy. Factors that were associated with increased mortality included: coexisting non-tuberculous mycobacteria (*NTM*) infection, COPD, increased age, low albumin, low activity on St George's Respiratory Questionnaire (SGRQ), increased MRC dyspnoea scores, and the presence of aspergillomas (especially bilateral) (81). A subset of these patients had fungal susceptibility information; patients with fully sensitive isolates had a 10-year survival of 68% in comparison to 46% in patients with any degree of azole resistance. Patients with pleural disease, cavitary disease and bilateral disease also had poorer outcomes compared to patients with nodules and intraluminal cavities, evident after 2 years.

Recent ERS guidelines have stratified the diagnosis of CPA (82), though an unbiased cluster analysis failed to separate patients by clinical criteria, suggesting while it can be useful to categorize patients, in reality there is a spectrum of disease (83). The diagnosis of chronic cavitary pulmonary aspergillosis (CCPA) requires the progression (enlargement and coalescence) of pleural or lung cavities with or without mycetomas or pleural thickening over ≥3 months with associated symptoms and either positive Aspergillus IgG serology or positive culture. Chronic fibrosing pulmonary aspergillosis (CFPA) presents as extensive fibrotic lung destruction with or without cavities and mycetomas, often this is the end result of untreated CCPA. Important differential diagnoses to exclude are mycobacterial infection, endemic mycoses (histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis) if there is an appropriate exposure history, and malignancy. The setting of NTM and CPA co-infection is not uncommon (84) and can be difficult to treat as rifampicin induction of cytochrome p450 enzymes can result in reduced azole levels (85).

Risk of subacute invasive aspergillosis (SAIA), previously chronic necrotising pulmonary aspergillosis, where symptoms and radiology progress over 1 to 3 months (86), is increased in patients with malnutrition, alcoholism, diabetes mellitus, prolonged steroid exposure, COPD, connective tissue disease, and HIV (87-89). Differential diagnoses include malignancy, vasculitides, and pulmonary infarctions. CPA can also present as aspergillus nodule and solitary aspergilloma, usually requiring surveillance rather than treatment in these contexts.

Aspergillus IgG is highly specific for CPA diagnosis in the context of progressive radiology and symptoms, with one small study reporting 100% positive predictive value (90). Two assays are commonly used to measure precipitating antibodies; the Platelia and Immunocap assays are similar at cut off values of >10 AU/mL and >40 mg/L respectively when discriminating between CPA and ABPA or other diseases (91), though the Immunocap appears to have a greater working range. The Platelia test had previously been shown to have a sensitivity of 90.2% to 93.8% and specificity of 99.5–100% when compared to healthy controls (though this reduced to 54–60% in comparison to patients with Aspergillus colonisation) (92), similarly the Immunocap has 98% sensitivity and 84% specificity with a cut off of 50 mg/L in a Japanese study of proven CPA (93). False negatives can appear in the context of hypogammaglobulinaemia, selective inability to produce *A. fumigatus* IgG (associated with functional deficiencies in pneumococcal and Haemophilus antibody), and non-aspergillus infections; e.g., with endemic mycoses or *Scedosporium* species. While there is little direct data, there is a suggestion that IgG titres reduce with successful treatment (94).

The value of serology and PCR is less well established

in the context of CPA in comparison to IFA. A recent study evaluated BALF of CPA patients (95). They found that GM with a cut off of 0.5 ODI had a sensitivity of 78% and specificity of 90%, BDG (using Fungitec G test) with a cut off of 100 ODI, a sensitivity of 78% and specificity of 73%, and Aspergillus PCR sensitivity of 67–87% and specificity or 67–84%. If GM and BDG were used in combination, sensitivity was 67%, specificity 98%, positive predictive value 90% and negative predictive value 93%. Overall it appears that there is an inverse correlation between serum GM levels and Aspergillus IgG state when comparing aspergilloma, CPA, and IA (96).

CT is an important modality in diagnosing CPA syndromes, and repeat CT 6 months after commencing treatment has been shown to correlate with outcomes (97). Pleural and cavity wall thickness reduced with treatment, and resolution of mycetoma was also associated with clinical improvement, whereas changes in cavity volume, pericavitary infiltrates and consolidation were not.

The treatment of CPA is often long-term and can sometimes be poorly tolerated. Often the patients are frail or have significant comorbidities that may shorten their lifespan. Success rates are relatively poor with treatment goals often being symptom control rather than cure. Treatment is for a minimum of 6 months and often lifelong (98). A combination of symptom review, CT and serology can be used to guide treatment.

Oral voriconazole has a 53% success rate in treating SAIA and 14% success in CCPA (99), as determined by ≥50% radiological resolution and presumed mycological eradication. This was associated with subjective improvement in clinical symptoms assessed by visual analogue scale and reduction in serological response. This compares with historic studies with itraconazole considered stabilization of disease a success and reported approximately 20–30% radiological improvement (100,101), though it is clearly superior to supportive care (102). Posaconazole has a response rate of 61% at 6 months, and 46% at a year, where non-progression was considered a response (94). Retrospective analysis of SGRQ determined clinical symptoms suggests that posaconazole is superior to voriconazole which is in turn superior to itraconazole, though this must be viewed with caution without randomised control trial (RCT) head to head trials (103). It should be noted that many of these studies have heterogeneous participants and patients with SAIA have better treatment responses than those with CCPA, with only recent studies separating the two entities.

An RCT comparing voriconazole with micafungin indicated similar efficacy with micafungin having fewer adverse events (104). A further RCT show no difference in clinical response to CPA between caspofungin and micafungin, suggesting that this is little difference in the echinocandins (105). Additionally, case series have shown caspofungin can be effective in the scenario of progressive symptoms despite oral azole or with azole intolerance (106).

Liposomal amphotericin has been used as both induction therapy, for recalcitrant disease and in the setting or azole resistance. A case review indicated 74% of treated patients had clinical improvement (composite of MRC dyspnoea score and weight gain) after 6 months (107). A subset of these patients had recurrent courses of treatment with continuing symptom and serological improvement. Decline in renal function was widespread but only required cessation of therapy in 15% of cases, though this increased with repeated dosing.

Worryingly azole resistance, likely due to environmental fungicide use (108) has begun to emerge and has been associated with treatment failure (109-111), though it is unclear whether this can be reduced by ensuring appropriate therapeutic levels. Consensus expert opinion suggests the use of intermittent or continuous liposomal amphotericin or micafungin in the setting of pan azole resistance (112), and indeed where local resistance rates are >10% to begin treatment with liposomal amphotericin or with a voriconazole—echinocandin combination.

Azoles work by inhibiting fungal cytochrome P450, and can affect other drugs which are metabolized by human cytochrome p450 pathways, such as carbamazepine, so caution must be taken to take a full drug history and consider interactions before prescribing. Common azole adverse effects include hepatotoxicity, nausea, liver dysfunction, phototoxicity and visual disturbances. Measuring trough levels can be useful to minimise these side effects as well as ensuring therapeutic doses are being used. Polyenes (i.e., amphotericin) extract ergosterol from fungal cell membrane and the major side effect is renal failure, particularly when prescribed with other nephrotoxins. The echinocandins inhibit glucan and so cell wall synthesis. They are largely well tolerated with temporary infusion related fever and flushing being the commonest adverse event.

## Conclusions

Fungal lung infection incidence and prevalence has increased over the past few decades, probably as a result of increased

 

numbers of patients who are immunocompromised e.g., after transplant or on long term immunosuppressive agents such as high dose steroids. This has led to a cohort of patients with a spectrum of immune deficiencies that allow fungi to cause disease ranging from invasive infection with haematogenous spread to chronic indolent respiratory infection. These conditions can be difficult to diagnose with confidence and treatments can have significant toxicities particularly with prolonged consumption. It is important to have fungal pathogens in the differential of infective symptoms in the immunocompromised host and involve physicians familiar with treating them early during their course of treatment.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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