Fungal infections and critically ill adults

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Key points

The incidence of fungal diseases in critically ill patients is thought to be increasing, most commonly involving *Candida* and *Aspergillus* species.

Risk factors for invasive fungal infections include: immunocompromised states, including neutropaenia; intravascular or other catheters (especially if parenteral nutrition is involved); prostheses; anatomical barrier loss (for example, burns); broad-spectrum antimicrobial usage.

Delays in commencing antifungal therapies are associated with worse outcomes, and as a result of the difficulties associated with confirming fungal infections, empirical therapy is often commenced in high-risk patients.

Geographical variation in the prevalence of fungal species will affect the choice of antifungal therapy.

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Although there are many different species of fungi, relatively few are responsible for human illnesses. Fungal infections associated with critical illness are thought to be increasing in incidence, possibly as a result of the increasing population of immunocompromised individuals, more aggressive medical interventions and procedures, and increased use of anti-bacterial therapies.

Structure and classification of fungi

Fungi are eukaryotes (i.e. having membranes that cover the nucleus and other intracellular organelles); this makes them structurally similar to animals and plants, but different from prokaryotes such as bacteria. Fungi have rigid cell walls containing chitin, chitosan, mannan, and glucan. Fungi also have cell membranes structurally different from that of animals as they contain ergosterol rather than cholesterol.

The simplest subclassification of fungi responsible for human infections is as either moulds (e.g. *Aspergillus* species) or yeasts (e.g. *Candida* species). Under the microscope, yeasts are small rounded cells that can bud, while moulds demonstrate a stranded, filamentous appearance caused by hyphae. Some fungi can exist in both forms (these are said to be dimorphic, e.g. *Blastomyces*), and some yeasts can develop pseudo-hyphae (e.g. *Candida* species). When the hyphae of filamentous fungi develop a matted, intermeshed network, this is referred to as a mycelium.[1]

Fungi are slow-growing, with cell-doubling times often as long as days, which can affect the ability to identify clinically relevant infections. Reproduction may be sexual, asexual, or both; and may result in the production of 'daughter cells' or spores. Many fungi and spores are environmentally ubiquitous, for example, *Aspergillus* species are commonly found in soil, and their spores are prevalent in the atmosphere.

Several fungi are common human flora (for example, *Candida* occur within the human gut) or are able to colonize structures such as the gut, oropharynx, or upper and lower airways. It can sometimes be difficult to tell whether or not a positive fungal culture is indicative of invasive disease or simply the result of the capture of normal flora.

Fungal infections in the critically ill

A list of risk factors for fungal infections can be found in Table 1. Admission to intensive care unit (ICU) has been identified as a risk factor associated with invasive fungal infection, and there is evidence suggesting higher rates of non-infective fungal colonization and of horizontal transmission occurring within critical care areas. The fungi most commonly associated with infections in the critically ill are *Candida* and *Aspergillus*. Less common causes include *Zygomycetes*, *Histoplasma*, *Cryptococcus*, *Blastomyces*, and *Coccidioides*. These names often do not describe specific fungi, rather a species or class of fungi. As fungi are opportunistic, the list of rare examples identified as human pathogens continues to grow.

Symptoms associated with mycoses (diseases caused by fungi) are often non-specific generalized inflammatory responses (for example, pyrexia and tachycardia), or specific end-organ damage (for example, hypoxia or confusion). In neutropaenic or immunocompromised patients, white cell counts are often unhelpful. Cutaneous and mucous membrane stigmata can be associated with systemic fungal infections (for example, oral candidiasis, or cutaneous eschars caused by invasive *Aspergillus*), but these are uncommon. A high-index of suspicion is required to identify fungal infections, especially as delays in treatment are associated with worse outcomes.[2]

Candida

Candida species are responsible for the majority of fungal infections in critically ill patients, with *Candida albicans* being the most common organism in the UK. The *Candida* genus also

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Table 1 Risk factors thought to affect the incidence of fungal disease

Immunocompromise	Human immunodeficiency virus
	Haematological malignancy
	Haematopoietic stem cell transplant
	Neutropaenia
	Chemotherapy
	Immunosuppressant usage, for example:
	Solid organ transplant
	Long-term steroid usage
	Liver disease
	Diabetes
	Renal failure and haemodialysis
	Burns
	Malnutrition
Respiratory compromise	Suppurative diseases, for example:
	Cystic fibrosis
	Bronchiectasis
	Chronic obstructive pulmonary disease
	Tracheal intubation and mechanical ventilation
Invasive procedures	Central venous catheters
	Parenteral nutrition
	Urinary catheterization
	Intra-peritoneal dialysis catheters
	Implanted prosthetics and devices, for example:
	Heart valves
General	Increased use of broad-spectrum antibiotic therapy
	Gut lumen contamination of body compartments, for example:
	Faecal peritonitis
	Oesophageal perforation
	I.V. drug misuse

contains other species that cause human infection, including: *Candida tropicalis*, *Candida parapsilosis*, *Candida glabrata*, *Candida krusei*, and *Candida dublinsiensis*; these are collectively known as 'non-albicans' species. The incidence of non-albicans *Candida* varies with geographical location and overall appears to be increasing, possibly related to the increased use of the antifungal agent fluconazole, which might select out resistant non-albicans *Candida* species, such as *C. glabrata* and *C. krusei*.

Candida infections (candidiasis or candidosis) are mostly superficial, affecting mucous membranes or skin. Invasive candidiasis occurs when *Candida* enters the blood stream causing a candidaemia, and there is haematogenous spread to the liver, spleen, brain, eyes (causing endophthalmitis), or heart (causing endocarditis). Rates of nosocomial ICU blood stream infections caused by *Candida* vary between healthcare systems, with data from the USA suggesting that it is the fourth most common micro-organism responsible (5–10% of infections), while in European studies it is between the 6th and 10th most common cause. Estimates of the mortality associated with candidaemia vary, but may be as high as 40%. Infections related to non-albicans species have been associated with worse outcomes. *Candida* can affect organs and body cavities by direct spread. The peritoneum and thoracic cavity can both be infected after bowel or oesophageal perforation, or through colonization of intra-peritoneal dialysis catheters.[3]

Candida spp. are often isolated from respiratory secretions obtained from critically ill patients, although true infection of the lower respiratory tract is rare. Growth of *Candida* spp. from respiratory specimens alone should not prompt the use of antifungal therapy in most patients. Candiduria is also difficult to interpret and can represent conlonization of urinary catheters or the lower urinary tract in the absence of symptoms. Alternatively, *Candida* spp. may cause an ascending pyelonephritis frequently complicated by the development of fungal balls, or spread to the urinary tract by haematogenous dissemination. The presence of pyuria is of limited value in determining the significance of candiduria as it may represent bacterial co-infection in as many as 25% of cases. In severely immunocompromised patients, fever and candiduria may be a surrogate marker of disseminated disease and require treatment; in other patient groups removal of predisposing factors such as indwelling catheters may be sufficient.[4]

Candida commonly colonizes urinary catheters and intravascular devices (especially in the presence of parenteral nutrition) and removal of the indwelling device is often required to enable the eradication and cure of any associated infection. An often-debated topic is the need for central venous line removal in cases of candidaemia. In non-neutropaenic patients, there is evidence of improved outcomes after early line removal, regardless of the putative source. Where *C. parapsilosis* is the causative organism, line removal should be undertaken whenever possible as the organism is thought to form resistant biofilms.

The two most commonly cited complications of disseminated candidiasis are infective endocarditis and ocular involvement. This has led to recommendations that patients with candidaemia should undergo both echocardiography and dilated retinal examination. However, a more targeted approach has also been suggested whereby persistently positive blood cultures despite treatment and removal of an infected focus indicate the need to investigate for endovascular involvement. Although patients who report new visual disturbance should be prioritized for ophthalmological review, early ophthalmological review is required even in the absence of symptoms as infection may be clinically silent, especially in critically ill patients.[5]

Aspergillus

Aspergillus species are responsible for a range of invasive and saprophytic human diseases, and common, but non-infective, conditions such as allergic bronchopulmonary aspergillosis and allergic sinusitis. The lung is the most common site of true infection with *Aspergillus* spp. The formation of a simple aspergilloma (fungal ball) is regarded as being a saprophytic condition, with most other pulmonary infection involving varying degrees of tissue invasion. These include invasive pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis, chronic cavitatory aspergillosis, tracheobronchial aspergillosis, and *Aspergillus* bronchitis. Extrapulmonary aspergillosis can also occur, as a result of either haematogenous dissemination or contiguous spread (for example, sinus disease leading to cerebral involvement).[6]

Only a very few of the several hundred species of *Aspergillus* mould cause human disease, and of these *Aspergillus fumigatus* is the most common. Less common potential pathogens include: *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus nidulans*, *Aspergillus oryzae*, *Aspergillus glaucus*, and *Aspergillus versicolor*.

Aspergillus pneumonia typically presents with non-specific symptoms such as fever, cough, dyspnoea, and occasionally pleuritic pain or haemoptysis. Dissemination from the lungs to other organs may cause abscess/aspergilloma formation and angio-invasion. Angio-invasion occasionally results in pseudo-aneurysms that can rupture and bleed resulting in massive haemoptysis where the lungs are affected. Chest X-ray changes in pulmonary aspergillosis are typically non-specific and may include pleural infiltrates, cavitation, and rounded densities (pleural effusions are an uncommon finding). Chest CT imaging may identify features more specific to invasive *Aspergillus* infection (see later section on 'Diagnostic techniques').

Direct sampling of bronchial secretions/washings or of lung tissue may indicate the presence of *Aspergillus*. The presence of *Aspergillus* in respiratory secretions/washings alone cannot distinguish between colonization and true infection and must be interpreted in the context of the clinical condition of the patient. Lung histology is only rarely available, but can confirm the diagnosis by demonstrating the presence of septate, branching hyphae invading lung tissue. In neutropaenic patients the diagnostic yield of any cultures may be particularly low, and antifungal therapy specific to *Aspergillus* is often commenced on an empirical basis in patients with risk factors for fungal disease.

Zygomycosis

Zygomycetes are a *class* of fungus that includes several orders and species. The taxonomy of this group of fungi contains many synonymous or obsolete terms, but as the order *Mucorales* are most commonly involved in human infection, the terms 'mucormycosis' and 'zygomycosis' are often used interchangeably. The literature is confusing to interpret, and an up-to-date list of fungal terms can be found at www.doctorfungus.org. *Absidia corymbifera*, *Rhizopus arrhizus*, *Rhizomucor pusillus*, and *Mucor indicus* are the most commonly implicated species.

Zygomycosis is rare and may affect any organ, in particular the sinuses, brain, skin, lungs, and gastrointestinal tract. Angio-invasion and disseminated infection, with associated necrosis, are hallmarks of the disease. Prompt surgical debridement together with antifungal therapy may improve survival, although mortality rates are high.

Zygomycosis typically affects immunocompromised hosts, but also has a specific association with diabetic ketoacidosis where a classic rhinocerebral form can occur that carries a poor prognosis.

Cryptococcosis

Cryptococcus neoformans and *Cryptococcus gattii* are responsible for most cases of cryptococcosis, which is strongly associated with immunocompromise, and in particular human immunodeficiency virus (HIV) infection. As with tuberculous infections, cryptococci are known to remain dormant within lymph nodes.

Cryptococcosis primarily affects either the lungs or the central nervous system, but can result in disseminated infection affecting almost any organ. Pulmonary cryptococcosis can present as an infiltrative pneumonia, occasionally with associated pleural effusions or hilar lymphadenopathy. Pulmonary nodules may occur, which can cavitate or result in distal lung collapse, and chest X-ray appearances may be similar to those of lung cancer.

Cryptococcal meningo-encephalitis may develop slowly over weeks, presenting with fever and non-specific neurological symptoms including: headache, cranial nerve palsies, memory loss, meningeal irritation, and reduced consciousness. Cryptococcomas can develop, as can raised intracranial pressure, especially if hydrocephalus develops as a result of 'sludging' within the cerebrospinal fluid (CSF), cryptococcoma formation, or scarring. Even with optimal treatment the mortality associated with cryptococcal meningo-encephalitis is as high as 20%.

Blastomyces, *Histoplasma*, *Coccidioides*, and *Paracoccidioides*

Blastomyces dermatitidis, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Paracoccidioides brasiliensis* are thermally dimorphic fungi found in soil from the Americas (and in the case of *B. dermatitidis* also from Africa). These fungi are capable of causing self-limiting pneumonia when inhaled. In immunocompromised individuals haematogenous spread may affect the liver, bones, joints, brain, or skin.

Histoplasma may appear similar to *Pneumocystis jirovecii* yeasts and can cause a cavitating pulmonary disease that is similar in appearance to tuberculous lung disease. *Blastomyces* infections may cause granulomatous skin ulcers, and *Paracoccidioides* can result in palatal and oropharyngeal lesions with extensive erosion and tissue destruction.

In non-endemic areas diagnosing these infections is difficult because of the lack of availability of indirect laboratory tests and reliance on slow and relatively insensitive direct culture techniques. Propagating these organisms is hazardous to laboratory personnel and samples should be labelled as high risk with the relevant history attached. Consultation with a medical microbiologist is essential if infection with dimorphic fungi is suspected.

Pneumocystis pneumonia

There are different species of *Pneumocystis*, but they appear to be species specific, with *Pneumocystis jirovecii* affecting the human lungs. *Pneumocystis jirovecii* (also known as *Pneumocystis carinii*) was previously thought to be a protozoa but is genetically classified as a fungus. It demonstrates certain aspects that are different from those of other fungi, including a lack of ergosterol.

Pneumocystis pneumonia typically presents with gradually progressive dyspnoea, an unproductive cough (although in fact up to 30% of patients may expectorate), and a low-grade fever. It is commonly

associated with HIV seropositive individuals [specifically those with advanced disease or acquired immunodeficiency syndrome (AIDS)], cancer, or the administration of immunosuppressants (including after organ transplantion). Chest X-rays may reveal bilateral, proximal interstitial inflitrates; and pneumatocoeles and pneumothoraces are common findings. Dissemination beyond the lungs is rare. Person-to-person spread of pneumocystis pneumonia is suspected to occur, and isolation of patients is advisable.

Most antifungal agents are ineffective against *P. jirovecii*, and treatment involves co-trimoxazole, pentamidine, atovaquone, primaquine, dapsone, or clindamycin. There is some evidence that echinocandins may be active against the infection, in particular micafungin. Antimicrobial treatment of pneumocystis pneumonia is normally accompanied by the administration of steroids. Pneumocystis pneumonia has a high associated mortality, with estimates ranging from 20 to 60%.[7]

Table 2 Diagnostic techniques available for identifying fungal infections. *These tests may not be readily available in the UK. †Sputum induction with hypertonic saline may be useful, and the microscopic identification of pneumocystis pneumonia is thought to be most effective in patients with AIDS

Candidiasis	Microscopy/culture of sputum, BAL, urine, or other body fluids (or tissue samples) Blood culture Serum mannan and anti-mannan tests Serum assay for 1–3 beta-D-glucan Whole blood PCR Fundoscopy if eye involvement considered
Aspergillosis	Microscopy/culture of sputum, or other body fluids or tissue samples Serum or BAL assay for galactomannan Serum assay for 1–3 beta-D-glucan Whole blood PCR Chest CT imaging
Zygomycosis	Microscopy/culture of sputum, BAL, or other body fluids or tissue samples (including tissue scrapings and skin biopsies from necrotic lesions) Whole blood PCR (in some cases)
Cryptococcus	Microscopy/culture of CSF Blood and urine culture Antigen test on CSF or blood Chest X-ray
Blastomycosis	Microscopy/culture of sputum, BAL, urine, or pus Serum assay for 1–3 beta-D-glucan Urine antigen assay*
Histoplasmosis	Microscopy/culture of sputum, BAL, or pus Microscopy of blood smears Blood or bone-marrow culture Serum assay for 1–3 beta-D-glucan Antigen radioimmunoassay in blood, urine, CSF, or BAL
Coccidiomycosis	Microscopy/culture of sputum, CSF, joint aspiration fluid, or pus Serum assay for 1–3 beta-D-glucan Coccidioidin skin test* Serum latex agglutination test* Serum or CSF complement fixation test*
Paracoccidiomycosis	Microscopy/culture of sputum, pus, or tissue granuloma biopsies Antigen complement fixation test*
Pneumocystis pneumonia	Microscopy of sputum (after staining)† Sputum or BAL immunofluorescence and PCR Serum assay for 1–3 beta-D-glucan Chest X-ray and chest CT imaging

Diagnostic techniques

Fungi, or fungal invasion of tissues, can sometimes be seen directly under the microscope, and certain fungi can also be cultured using specialist culture plates, which can contain anti-bacterial elements. Where there is skin involvement, microscopy and culture of skin biopsies may help in identifying the organism.

Specialist tests can detect fungal elements including polymerase chain reaction (PCR) detection of fungal DNA, and galactomannan which is present in the cell wall of *Aspergillus* species and can be detected in blood and bronco-alveolar lavage (BAL) specimens. A list of potential microbiological investigations associated with different fungal infections can be found in Table 2. Serum inflammatory markers are non-specific for fungal infections.[8] Moderate increases in procalcitonin levels may assist in differentiating between fungal and bacterial infections, but procalcitonin has a low sensitivity for invasive fungal infections.[9]

Chest X-rays changes in fungal pneumonia are non-specific. In the case of *Aspergillus* lung disease the presence of aspergillomas or 'air crescent' formations on chest CT can be diagnostic if present (see Fig. 1). More common, but less specific, findings of *Aspergillus* lung disease on CT include nodules surrounded by a diffuse 'halo' of ground-glass appearance (the 'halo sign'), or pleural 'wedges' of consolidation.

Fundoscopy may reveal cotton-wool ball changes within the retina if candidal choroidoretinitis is present.

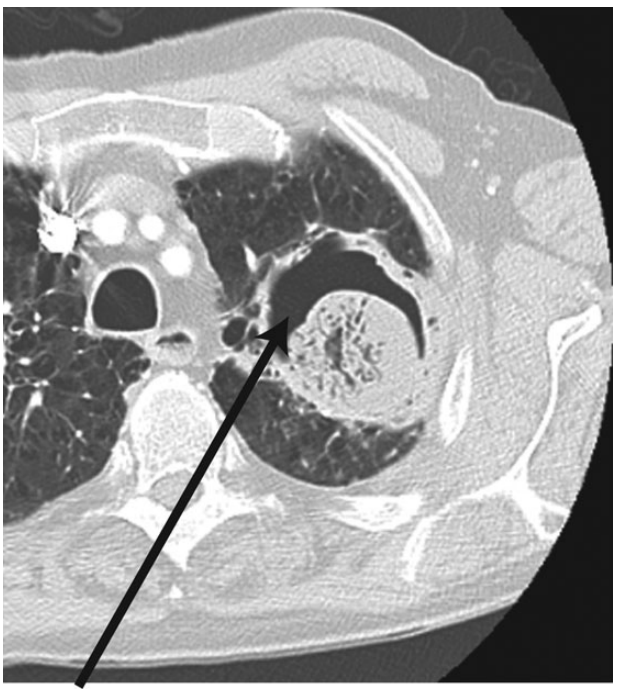

Fig 1 A case of *Aspergillus* lung disease showing the presence of diagnostic aspergillomas or 'air crescent' formations on chest CT.

Antifungal treatments

Antifungal agents work by a variety of mechanisms (see Fig. 2). A list of current antifungal agents can be found in Table 3. Targeted antifungal infection may include:

- Candidiasis: fluconazole; or if a resistant *Candida* species is likely: an echinocandin or an amphotericin.
- Aspergillosis: voriconazole, an amphotericin, or both.
- Zygomycosis: an amphotericin ± posaconazole.
- Cryptococcosis: an amphotericin with flucytosine, followed by fluconazole.

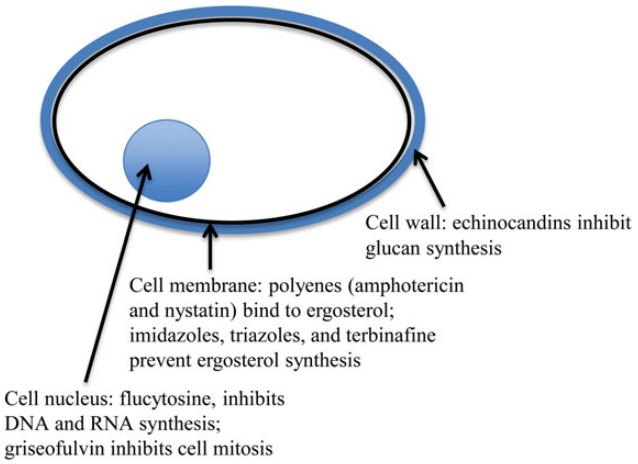

Fig 2 Mechanisms of action of antifungal agents.

- Blastomycosis: itraconazole, fluconazole, or an amphotericin (depending on the site and severity of the disease).
- Histoplasmosis: itraconazole or an amphotericin (possibly with steroids in acute pulmonary disease).
- Coccidioidosis: fluconazole or an amphotericin.
- Paracoccidioidosis: co-trimoxazole (fluconazole or an amphotericin if co-trimoxazole not tolerated).
- Pneumocystis pneumonia: co-trimoxazole (with steroids); alternatively, if co-trimoxazole is not tolerated: pentamidine or primaquine/atovaquone with clindamycin.

Amphotericin, an i.v. polyene antifungal, has the broadest range of antifungal activity, but usage is limited by side-effects, including nephrotoxicity, anaphylactoid reactions, electrolyte disturbance, and bone-marrow suppression. Liposomal amphotericin formulations are available (AmBisome® and Abelcet®) that have a reduced incidence of nephrotoxicity. Different formulations of amphotericin should not be stored together as their dosing regimens are very different and there is the potential for severe toxicity if conventional amphotericin is dosed in the same manner as liposomal amphotericin.

Echinocandins and azole antifungals are well tolerated, but both classes may have a tendency to promote varying degrees of liver dysfunction. Certain azoles prolong the QT interval particularly when used in combination with other drugs. Azoles also affect the cytochrome P450 causing drug interactions, for example, ciclosporin and rifampicin.

Antifungal agents may also be used as prophylaxis against invasive fungal infections in individuals with neutropaenia, patients treated with immunosuppressants after solid organ transplants, and patients with HIV who have low CD4 counts. Antifungal

Table 3 Treatments for fungal infections. *Although some echinocandins have activity against pneumocystis pneumonia, they are not commonly used treatments. Pneumocystis pneumonia antimicrobials are not included here, as they are not classical antifungal agents. †*Aspergillus terreus* is resistant

Category	Drug	Formulation	Main indication
Azoles (triazoles)	Fluconazole	PO/IV	*Candida albicans*
	Itraconazole	PO/IV	Balstomycosis, histoplasmosis, aspergillosis, candidiasis, cryptococcal meningitis
	Posaconazole	PO	*Aspergillus* (alternative treatment), zygomycosis, fluconazole-resistant *Candida* spp.
	Voriconazole	PO/IV	Invasive aspergillosis, non-albicans candidaemia, coccidioidomycosis, fluconazole-resistant *Candida* spp.
Azoles (imidazoles)	Ketoconazole	PO	All are limited to cutaneous or mucocutaneous fungal infections
	Miconazole	Topical/buccal	
	Econazole nitrate	Topical	
	Clotrimazole	Topical	
	Tioconazole	Topical	
Echinocandins*	Anidulofungin	IV	Candida species
	Caspofungin	IV	Most candida infections, potential salvage treatment for *Aspergillus*†
	Micafungin	IV	
Polyenes	Amphotericin B	IV	Active against most systemic fungal infections, including aspergillosis
	Liposomal amphotericin	IV	
	(AmBisome®)	IV	
	(Abelcet®)		
Others	Flucytosine	IV	Cryptococcal meningitis (used in combination with amphotericin)
Other topical antifungal agents	Amorolfine		
	Benzoic acid		
	Griseofulvin		
	Nystatin		
	Terbinafine		
	Undecanoates		

prophylaxis may reduce opportunistic infection with *Pneumocystis* (using reduced doses of co-trimoxazole), *Candida* (using fluconazole, echinocandins, or an amphotericin), and *Aspergillus* (using voriconazole or an amphotericin). Anti-candidal prophylaxis with fluconazole may be used after upper and lower gastrointestinal perforation, but only limited evidence exists to support this.

Empirical treatment is required when high-risk patients develop evidence of severe sepsis or severe respiratory compromise. Broad-spectrum antifungals such as an echinocandin are advised, and amphotericin may be required if a resistant species or pulmonary aspergillosis is possible.

Declaration of interest

None declared.

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Please see multiple choice questions 9–12.