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Invasive mould infections in the ICU setting: complexities and solutions

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Infections caused by filamentous fungi represent a major burden in the ICU. Invasive aspergillosis is emerging in non-neutropenic individuals with predisposing conditions, e.g. corticosteroid treatment, chronic obstructive pulmonary disease, liver cirrhosis, solid organ cancer, HIV infection and transplantation. Diagnosis is challenging because the signs and symptoms are non-specific, and initiation of additional diagnostic examinations is often delayed because clinical suspicion is low. Isolation of an *Aspergillus* species from the respiratory tract in critically ill patients, and tests such as serum galactomannan, bronchoalveolar lavage 1–3-β-D-glucan and specific PCR should be interpreted with caution. ICU patients should start adequate antifungal therapy upon suspicion of invasive aspergillosis, without awaiting definitive proof. Voriconazole, and now isavuconazole, are the drugs of choice. Mucormycosis is a rare, but increasingly prevalent disease that occurs mainly in patients with uncontrolled diabetes mellitus, immunocompromised individuals or previously healthy patients with open wounds contaminated with Mucorales. A high proportion of cases are diagnosed in the ICU. Rapidly progressing necrotizing lesions in the rhino-sinusal area, the lungs or skin and soft tissues are the characteristic presentation. Confirmation of diagnosis is based on demonstration of tissue invasion by non-septate hyphae, and by new promising molecular techniques. Control of underlying predisposing conditions, rapid surgical resection and administration of liposomal amphotericin B are the main therapeutic actions, but new agents such as isavuconazole are a promising alternative. Patients with mucormycosis receive a substantial part of their care in ICUs and, despite advances in diagnosis and treatment, mortality remains very high.

Introduction

Fungal infections represent a major burden in the critical care setting, incurring increased morbidity and mortality in a vulnerable population. The ICU team faces the challenge of invasive mould infections in both 'conventional' cases in neutropenic individuals but also, increasingly, in non-neutropenic patients. *Candida* infections, *Aspergillus* infections and mucormycosis caused by members of the Mucorales order are the most common infections, each of which requires a different diagnostic and therapeutic approach. The purpose of this review is to provide a practical guide to the basic aspects of mould infections (*Aspergillosis* and mucormycosis) in the critical care setting.

Invasive aspergillosis

Invasive aspergillosis (IA) is an opportunistic infection that occurs mainly among patients with haematological malignancies, most notably during prolonged periods of neutropenia, but also in subjects with solid tumours, critical illness or HIV/AIDS, and in those who have undergone allogeneic stem cell transplantation or solid organ transplantation.[1,2] In recent years, however, IA has increasingly been recognized as an emerging disease in non-neutropenic individuals and in patients admitted to the ICU, even in the apparent absence of a classic predisposing immunodeficiency.[3–8] Although not uncommon in immunocompetent patients, the features of IA in this setting differ substantially from those in neutropenic patients and its epidemiology, clinical characteristics, outcomes and prognosis are not well known. The incidence of IA in the ICU ranges from 0.3% to 5.8%[4,5] with an overall mortality rate of >80%.[3,9]

A number of recent case series and single-centre cohort reports have documented the expansion of patient populations at risk for IA beyond those groups conventionally regarded as high risk. These include patients with COPD and other chronic lung or connective tissue diseases requiring corticosteroid therapy, decompensated liver cirrhosis, and solid cancer with or without treatment.[10,11]

Diagnosis of IA in non-neutropenic critically ill patients is challenging because the signs and symptoms are non-specific, and

initiation of additional diagnostic examinations is often delayed because clinical suspicion is low. Early diagnosis and timely therapeutic intervention require a high level of awareness and suspicion. Rates of IA in ICUs vary in different regions of the world, likely due to differences in the types of patients admitted to the ICU for treatment and the environmental quality of the air. A greater understanding of the population at risk, and the spectrum of symptoms caused by IA in non-neutropenic patients, may contribute to improved outcomes for this potentially treatable disease.

Epidemiology

In the critical care setting, *Aspergillus* can be harboured in poorly maintained ICU ventilation and water systems, as well as in various types of equipment. However, it is difficult to discriminate between colonization and infection when IA is isolated from the patient. An increased incidence of IA in the ICU has been documented, but with different rates among subsets of ICU patients. A high prevalence (17%) of IA has been observed in a cohort of 67 patients with severe hospital-acquired pneumonia admitted to the ICU.[12] Among 40 critically ill patients with confirmed H1N1 influenza infection, 9 (23%) developed IA 3 days after ICU admission.[13] Retrospective, autopsy-controlled studies have revealed interesting results. Roosen *et al.* analysed causes of death in the ICU and observed 15 cases of IA, 5 of which were undiagnosed before death, in a series of 100 autopsies.[14] In a study comparing neutropenic and non-neutropenic patients with a diagnosis of IA over a 6 year period, Cornillet *et al.* found a mean number of 15 cases of IA per year, of which approximately one-half occurred in the ICU.[6] In an Italian study conducted in two mixed ICUs over 2 years, the incidence of IA was 0.2%, far lower than in other reports from similar ICUs.[15]

Risk factors

Risk factors for IA in non-neutropenic patients admitted to the ICU include prolonged treatment with corticosteroids before ICU admission, COPD, liver cirrhosis with prolonged ICU stay (>7 days), solid organ cancer, HIV infection and lung transplantation.[16–19] However, many of these factors are frequent among non-neutropenic critically ill patients. One of the intriguing hypotheses proposed to explain a depressed immune response in the apparently immunocompetent patient with multiorgan dysfunction relates to the biphasic response to sepsis in which the initial hyperinflammatory phase is followed by relative immunoparalysis. This latter process is characterized by neutrophil deactivation, and may place the patient at risk for developing opportunistic infections such as IA.[20] Immunosuppression has been described as a late stage of the biphasic response to sepsis and multiple organ failure syndrome.[21]

One of the most important risk factors for IA in non-neutropenic patients is COPD.[7] Patients with COPD are susceptible to *Aspergillus* colonization of the lower tract of the respiratory airway, and under particular circumstances this may lead to invasive infection.[22] Patients with COPD present with alterations in lung structure, impaired immunological response, reduced mucociliary clearance and mucosal lesions. Moreover, they are prone to frequent hospitalization, broad-spectrum antibiotic treatment and invasive procedures. All these factors could explain the high incidence of aspergillosis in COPD.[7] Of note, patients with COPD are frequently treated with corticosteroids and both inhaled and systemic therapy have been described as a major risk factor for aspergillosis.[23,24] Steroids can accelerate the *in vitro* growth of *Aspergillus* spp. since both innate and acquired immune responses are impaired.[25] Vandewoude *et al.* defined a total daily dose $\geq$20 mg of prednisone or equivalent as a criterion for defining cases of IA.[26] Both compensated and decompensated cirrhosis have been described as risk factors for IA, and impaired phagocytosis has been proposed as a possible explanation for heightened risk in these groups.[27,28] Diabetes has been observed as another risk factor for IA,[26] possibly due to impaired innate and acquired immunity caused by hyperglycaemia.[29] Several authors have reported alcoholism and malnutrition as other possible risk factors for IA.[26,30] Regarding environmental factors, the concentration of *Aspergillus* spores in the air is another important factor and high levels have been associated with individual cases and outbreaks in ICUs.[31] It may also be possible that strains of *Aspergillus* that produce high levels of elastase are associated with a higher risk of invasion.[32,33]

Patients in the ICU are subjected to multiple therapies (e.g. broad-spectrum antibiotics, mechanical ventilation) and/or manoeuvres (e.g. insertion of central venous catheters), which may affect the immunological defence system. Even though some of these could contribute to patients' risk status, additional factors may be required for the development of IA.[5,16,30]

Clinical diagnosis and case definition

Clinical manifestations of IA (e.g. fever, cough, purulent sputum) may initially be indistinguishable from bacterial bronchopneumonia.[34] Recovery of the same *Aspergillus* species from several respiratory samples in the course of antibiotic-resistant pneumonia in patients with relevant risk factors is clearly suggestive for a diagnosis of IA.[10] It has therefore been proposed that isolation of an *Aspergillus* species from the respiratory tract in critically ill patients with risk factors (e.g. COPD after corticosteroid exposure, severe underlying disease) and clinical features of pneumonia should indicate a probable case of IA. The clinical significance of isolating *Aspergillus* conidia in respiratory samples remains unclear, and differentiating true infection from simple colonization can be difficult. Therefore, once the fungus is detected in a respiratory sample, the decision to start empirical antifungal treatment should be based on the patient's current clinical status and on the presence or absence of risk factors for the development of acute pulmonary aspergillosis.

The presence of a persistent pulmonary infection despite broad-spectrum antibiotics, or abnormal thoracic imaging by CT scanning, together with one or more risk factors should trigger further diagnostic exploration by the testing of respiratory secretions and/or laboratory markers. Invasive infections in patients with negative cultures might be supported by positive serological and molecular markers such as galactomannan (GM) antigen testing and *Aspergillus* PCR, which requires at least two sequential positive samples. Radiological findings can be non-specific in non-neutropenic patients, and of the typical imaging findings observed in neutropenic patients, the air crescent sign is seen only in a small proportion of cases, while the halo sign is very rarely observed. The halo sign and air crescent sign have a high sensitivity (80%) and

Table 1. Clinical algorithm for the diagnosis of IA in non-neutropenic patients in the ICU[42]

Category	Host factor	Clinical presentation	Mycological evidence
Proven IA	• Not required	• Not required	• Pathology evaluation showing compatible hyphae and associated tissue damage *and* • Culture showing *Aspergillus* in specimen obtained by a sterile procedure from a normally sterile site
Probable IA	At least one of the following: • Glucocorticosteroid treatment[a] • Neutrophil abnormality[b] • Chronic airway abnormality[c] • Decompensated cirrhosis • Treatment with recognized T-cell immunosuppressant[d] • Haematological malignancies/HSCT • Solid organ transplantation • HIV • Severe influenza	• And clinical or radiological abnormalities consistent with a pulmonary infectious disease process that are otherwise unexplained	At least one of the following non-definitive tests: • Cytology, direct microscopy and/or culture showing *Aspergillus* species in a lower respiratory tract specimen • GM in serum $\geq$0.5 and/or in BAL $\geq$0.8

GM, galactomannan; HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis.
[a]Glucocorticosteroid treatment with prednisone equivalent of $\geq$ 20 mg/day.
[b]Inherited neutrophil deficiency, absolute neutrophil count of $\leq$ 500 cells/mm^3.
[c]Chronic obstructive lung disease, bronchiectasis.
[d]Calcineurin or mTOR inhibitors, blockers of TNF and similar antifungal immunity pathways, alemtuzumab, nucleoside analogues during past 90 days.

specificity (60%–98%) in thoracic CT scans of neutropenic patients.[17,35] In non-neutropenic patients, a lower sensitivity (5%–24%) has been reported in the literature.[36,37] Bronchoscopy manifestations are also non-specific in non-neutropenic patients, with a lack of consistent features on endoscopy.[37]

The diagnosis of IA remains problematic. The lack of specific criteria for diagnosing IA in non-neutropenic patients hampers timely initiation of appropriate antifungal therapy and may therefore compromise chances of survival.[38–41] Recently Blot *et al.*[42] externally validated a clinical diagnostic algorithm that aims to discriminate colonization from probable IA in ICU patients with *Aspergillus*-positive endotracheal aspirate cultures (Table 1).

Microbiological diagnosis

The microbiological diagnosis of aspergillosis can be achieved using conventional and molecular approaches, including antigen detection and PCR assays.[43] Conventional culture methods are essential for isolating and identifying the aetiological agent, while identification is largely based on an accurate analysis of the macro- and microscopic features of the colonies. Size, colour and shape of the colony, microscopic visualization of conidiophores and conidial heads, morphology, size and colour of the conidia are important features for identifying the isolate at the species level.[43,44] More recently, DNA sequencing and the MALDI-TOF MS proteomic approach have been shown to be useful tools to identify non-sporulating isolates or isolates with atypical morphology.[45–47]

The Platelia *Aspergillus* enzyme immunoassay (Bio-Rad Laboratories, Redmond, WA, USA) reveals the presence of GM, a polysaccharide of the outer cell wall layer of *Aspergillus*, in patients with suspected aspergillosis.[43,48] GM can be detected in body fluids, but serum levels in non-neutropenic patients appear to be inaccurate, first because circulating neutrophils are able to clear the antigen, and second, due to various causes for false-positivity.[40] Meersseman *et al.*[49] demonstrated a high sensitivity and specificity of GM in bronchoalveolar lavage (BAL) fluid for the diagnosis of IA. Notably, the sensitivity of BAL GM was 88%, in contrast to 40% for serum GM. GM detection in BAL is therefore a valuable tool for the diagnosis of IA in non-neutropenic patients.[49]

Therapeutic approaches

Prompt and appropriate antifungal therapy is of critical importance for limiting the mortality rate from IA in ICU patients, which ranges between 60% and 90%.[16] Hence, patients without classic risk factors (i.e. COPD, steroids and immunosuppressive therapy, hepatic failure, ICU-related immunoparalysis) should start adequate antifungal therapy upon suspicion of IA, before obtaining definitive proof of infection. Early initiation of first-line therapy, at the stage of possible infection, was reported to improve outcomes in a retrospective analysis of factors predicting mortality in a series of 289 patients with possible, probable or proven IA.[50] However, high-quality studies specifically in ICU populations are generally lacking, and data from non-ICU settings is often the basis for treatment decisions, as discussed in the article 'New pharmacological opportunities for the treatment of invasive mould diseases' in this Supplement.[51]

In contrast to patients with febrile neutropenic episodes, there is no consensus about the exact time frame for starting empirical therapy, without any diagnostic support, in other categories of critically ill patients at risk of IA.[52] In a 6 year French survey, non-neutropenic patients with IA were less likely to exhibit symptoms suggestive of the disease but the sensitivity of microbiological sampling, antigenaemia and thoracic CT findings were similar to those

Table 2. Treatment of IA in non-neutropenic patients in the ICU

Setting	First choice	Alternatives
Primary therapy	Voriconazole (6 mg/kg q12h iv on day 1, then 4 mg/kg q12h iv) *or* Isavuconazole (initial dose 372 mg q8h po or iv × 6 doses for 48 h; maintenance dose 372 mg/day po or iv)	Liposomal amphotericin B (3–5 mg/kg/day iv) *or* Posaconazole (300 mg iv bid on day 1, then 300 mg/day iv) *or* Caspofungin 70 mg loading dose, then 50 mg/day
Salvage therapy	Combination of voriconazole plus anidulafungin	

bid, twice a day; iv, intravenous; po, per os (orally); q8h, every 8 h; q12h, every 12 h.

seen in neutropenic hosts.[6] Therefore, a pre-emptive approach in non-neutropenic patients, based upon microbiological biomarkers (GM, *Aspergillus* PCR and 1,3-β-D-glucan assay, as a screening strategy), may be helpful and should be implemented early for prompt detection and treatment of invasive fungal infections in the ICU.[11]

Three classes of antifungal agents are available for the treatment of IA: azoles (isavuconazole, voriconazole, posaconazole, itraconazole), amphotericin B and echinocandins (Table 2). Current guidelines recommend voriconazole as first-line treatment for IA, including for critically ill patients in whom intravenous administration is preferable.[53] During the last 10 years, voriconazole use has progressively become widespread. A key study driving the adoption of voriconazole was a randomized controlled trial published in 2002, in which 277 patients with IA, mainly affected by haematological diseases, showed significantly higher survival rates and fewer severe adverse events with voriconazole versus amphotericin B.[54] A large retrospective cohort study investigating risk factors and outcomes in ICU patients with IA (excluding those with classic risk factors) showed that a 1 day delay in starting effective antifungal therapy was associated with a mean of 1.28 days longer stay and a 4% increase in total costs per day ($P < 0.001$).[55] Voriconazole was the most frequent antifungal prescribed and its use appeared to improve these outcome measures.[55] Itraconazole is considered a second-line agent for the treatment of IA, particularly in severely ill patients. Use of oral itraconazole in non-life-threatening infections where the patient has been already stabilized with a more potent agent has been described.[56] Posaconazole is a broad-spectrum triazole with anti-*Aspergillus* activity similar to that of voriconazole but limited clinical experience, and (until recently) the absence of intravenous formulations has reduced its applicability in critically ill patients.

Isavuconazole, a new triazole agent, can be given once-daily and offers a wider spectrum of antifungal activity than voriconazole, including activity against most Mucorales infections. A large randomized, double-blind trial has demonstrated non-inferiority for isavuconazole versus voriconazole in terms of all-cause mortality when used as primary treatment for invasive fungal disease caused by *Aspergillus* species or other filamentous fungi, with a superior safety profile.[57]

Before the introduction of voriconazole, amphotericin B was the mainstay of treatment for IA. Development of lipid formulations improved the poor tolerability associated with the deoxycholate formulation, but the optimal dosage remains unconfirmed.[58] High-dose liposomal amphotericin B (10 mg/kg/day) does not improve outcomes but may increase nephrotoxicity.[59]

All echinocandins have been shown to exert *in vitro* and *in vivo* activity against *Aspergillus* spp. but only caspofungin is approved for the treatment of IA, in patients who are intolerant to first-line therapy. Although still not approved, the other two echinocandins (anidulafungin and micafungin) are used in clinical practice, particularly when non-neutropenic patients are involved. In breakthrough IA and in refractory disease, combination therapy (e.g. echinocandin plus voriconazole or liposomal amphotericin B) may be considered.

Outcome and prognostic factors

Only a small number of clinical studies have investigated the outcome of IA in critically ill patients. Different studies are difficult to compare due to the absence of specific clinical signs, variations in diagnostic criteria and inconsistency with which coexisting diseases are recognized as risk factors.[16] Mortality rates also vary. The overall mortality rates for IA are ∼17%, based on US national data, but mortality is higher in cases of *Aspergillus* pneumonia or in immunocompromised patients with IA.[59] Specifically, mortality rises to 25% in *Aspergillus* pneumonia, while in patients with blood or lymphoid tissue malignancies, bone marrow transplant recipients or liver transplant recipients, mortality rates in IA are 49%, 80% and 90%, respectively.[59] It should be noted that the immune status of critically ill patients, as well as other underlying conditions, are important determinants of the type of fungal infection that may develop, and for immunodeficient patients the infection is usually invasive. Thus, patients receiving steroids are at increased risk of developing cavitating lesions and aspergillomas. In a retrospective analysis of fungal infections in non-neutropenic patients, Garbino *et al.*[60] showed a mortality rate of 57.1% for patients with IA.

Various studies have examined prognostic factors, but isolation of *Aspergillus* in critically ill patients is associated with high mortality, irrespective of invasion or colonization.[11] Overall, it appears that the mortality rate in IA is significantly higher in non-neutropenic patients than in neutropenic individuals.

Mucormycosis

Mucormycosis is a fungal infection caused by different fungi of the order Mucorales, not only by those belonging to the genus *Mucor*. In

1978, Agger and Maki first drew attention to mucormycosis as a complication of critical care, reporting three previously non-immunocompromised patients who developed mucormycosis after treatment with steroids and antibiotics.[61] It is an uncommon but very severe disease, progressively reported in the last 20 years, and a high proportion of cases are diagnosed or treated in ICUs.[62–65]

Epidemiology

In a population-based study carried out in Spain in 2005, the rate of mucormycosis was 0.43 cases/1 000 000 inhabitants and 0.62 cases/100 000 hospital admissions.[66] In France, cases increased from 0.7/million inhabitants in 1997 to 1.2/million inhabitants in 2006.[67] In a tertiary care centre in India, the number of cases per year increased from 13 in 1990–99 to 50 in 2006–07.[68] Other reports have also indicated an increase of mucormycosis in recent years.[69,70] Epidemiological data specifically related to the ICU are lacking, but mucormycosis is frequently reported as individual case reports or as small series in ICUs.[62,65,71] The analysis of data from one centre found that 37% of mucormycosis cases were diagnosed in patients treated in the ICU (Emilio Bouza, CIBERES, personal communication).

Risk factors

Mucormycosis occurs mainly, but not exclusively, in immunocompromised patients with haematological malignancies, solid organ transplant recipients and patients with other immunodeficiencies, as well as in patients with diabetes mellitus. It can also occur following trauma or invasion of wounds covered with contaminated dressings, e.g. in the ICU. One outbreak of gastric mucormycosis in ICU patients reported in Spain arose in association with the use of contaminated wooden tongue depressors in critically ill patients.[72]

Clinical diagnosis and case definition

Manifestations of pulmonary mucormycosis are frequently fever and unresolving pulmonary infiltrates, despite the use of broad-spectrum antibiotics.[73,74] Respiratory mucormycosis may involve the lung parenchyma and the pulmonary vascular system but also the bronchial tree and trachea.[75] Radiological signs of pulmonary mucormycosis may be indistinguishable from those of IA or from neoplastic or inflammatory diseases. Ring-halo signs with air crescents may be indicative of mucormycosis in chest CT. The utility of positron emission tomography or CT scanning is still not definitively established but preliminary data shows uptake of [^{18}F]fluorodeoxyglucose[76,77] in invasive fungal infections.

Rhino-cerebral mucormycosis remains an important clinical presentation of mucormycosis, particularly in Asia and in patients with diabetes mellitus. Necrosis evolves rapidly, although cases of chronic slowly evolving lesions in immunocompetent hosts are occasionally reported.[78] Mucormycosis complicating wound infections or other skin lesions, including intravenous needle punctures, is well known and should be suspected in the presence of progressive necrosis of any extent. These may occur in traumatic wounds in completely immunocompetent hosts, such as patients in the ICU,[67,79] but also in immunocompromised patients of different types. In a European series reported by Skiada *et al.*[80] the most common manifestations of mucormycosis were pulmonary (30%), rhino-cerebral (27%), soft tissue (26%) and disseminated disease (15%).

Microbiological diagnosis

As discussed in 'Early diagnosis of mould infections and disease' in this Supplement,[81] the detection of both GM and 1–3-β-D-glucan is futile in mucormycosis because Mucorales do not produce these biomarkers.[82] A recently reported technique consists of quantifying Mucorales DNA in serum by PCR. It combines three quantitative PCRs to identify *Mucor/Rhizopus*, *Lichtheimia* and *Rhizomucor*[83,84] and can be positive many days before the appearance of common clinical manifestations. Confirmation of the utility of this technique will require experience in a larger series of cases.

However, confirmation of the diagnosis requires a positive culture from tissues that are ordinarily sterile, based on samples that have been obtained under sterile conditions. The combination of a clinically compatible setting with positive clinical samples obtained from non-sterile samples, such as respiratory secretions, makes the diagnosis only probable.[85] Tissue biopsy is essential, and the presence of broad, non-septate hyphae invading the tissues and vessels, with right angles and a ribbon-like appearance, is adequate to confirm the diagnosis.[86] In the case of pulmonary infections, samples may be obtained by open pulmonary resection but also by transthoracic CT-guided procedures and, in the case of rhino-cerebral forms, by samples obtained through nasal endoscopy.[87–89]

Samples must be approached carefully in the clinical microbiology laboratory and should not be triturated in preparation for culture. Alternatively, direct small fragments obtained with a scalpel can be examined and cultured to obtain a better yield. Calcofluor white examination is highly recommended, followed by culture and species identification. MALDI-TOF is currently a useful alternative to conventional methods for species identification,[90,91] as are molecular techniques performed either on isolates or in tissue samples.[92–94] Finally, antimicrobial susceptibility testing of antifungal agents against Mucorales isolates is an important part of the responsibilities of the microbiology laboratory.[95,96] *Mucor* isolates are largely susceptible to amphotericin B, posaconazole and isavuconazole, but not to fluconazole, voriconazole or candins.

Therapeutic approaches

Rapid application of treatment measures in mucormycosis is associated with reduced mortality.[97–101] Management strategies are similar for patients treated in the ICU or elsewhere (see 'New pharmacological opportunities for the treatment of invasive mould diseases' in this Supplement).[51] Three interventions must be combined: correction of underlying conditions where feasible, surgical resection when possible and antifungal therapy.

Regarding the underlying conditions, the correction of hyperglycaemia in diabetic patients, the reversal of ketoacidosis, and tapering of corticosteroids and immunosuppressive agents are among the recommended measures. Shortening the duration of neutropenia by granulocyte colony-stimulating factor is also recommended by ESCMID and the European Conference on Infections in Leukaemia[86,102] but the level of evidence demonstrating efficacy is minimal.

Surgery is a key element in the management of mucormycosis, particularly for rhino-cerebral forms and for mucormycosis of skin and soft tissues. Repeated surgical intervention is frequently necessary to achieve surgical control, with sequential resections. The role of surgery is less clear for pulmonary mucormycosis in

patients with haematological conditions and should be decided on an individual basis in patients with disseminated disease. Overall, surgery associated with antifungal agents improves mortality rates compared with medical treatment alone and is beneficial even when full resection of necrotic invaded tissue cannot be achieved.[76,102–107]

The role of specific drugs in the treatment of mucormycosis is described in 'New pharmacological opportunities for the treatment of invasive mould diseases' in this Supplement.[51] In brief, lipid formulations of amphotericin B, and particularly liposomal amphotericin B, are presently the mainstay of antifungal treatment of mucormycosis. Posaconazole is active *in vitro* against Mucorales and is considered a second-line drug, recommended for salvage therapy. Isavuconazole is a new triazole derivative, which is active against moulds of the order Mucorales, with better tolerance than amphotericin B, and can be used for the treatment of mucormycosis.

Other treatments

The use of adjunctive iron chelators, such as deferasirox or deferiprone, is still associated with contradictory data and, at present, neither agent is recommended as adjunctive treatment.[108,109] The use of hyperbaric oxygen is not currently recommended for routine use. It may be beneficial in rhino-cerebral forms in diabetic patients but is less clearly of benefit in haematological patients with pulmonary forms of the disease.[86,102,110]

Outcome and prognostic factors

Data regarding outcomes specifically relating to mucormycosis in the ICU are not available, but despite recent advances in diagnosis and treatment, the overall mortality associated with mucormycosis is estimated to be between 22% and 59%[80,111–115] depending on the location and extent of the disease, underlying condition of the patient and the speed in which proper treatment is administered.[99]

Conclusions

Invasive filamentous fungal infections are very severe infections that may be acquired in the ICU or, when acquired elsewhere, may require critical care. Their diagnosis and management represents a challenge for clinicians. The two main infections are IA and mucormycosis, which may occur as non-resolving pneumonias or as invasive extrapulmonary infections, particularly in skin and soft tissue, rhino-sinusal regions or other areas. The complex underlying conditions in these patients and the non-specific nature of symptoms can confound identification and lead to underdiagnosis. Isolation of *Aspergillus* or Mucorales in clinical samples may be insensitive or non-specific and the confirmation by biopsies showing tissue invasion is not always feasible. Indirect, non-tissue based, diagnostic tests are still in development and cannot yet provide a rapid, conclusive diagnosis or exclude these infections in most situations. Voriconazole, amphotericin B and isavuconazole are the drugs of choice for the treatment of IA, whilst amphotericin B, posaconazole and isavuconazole are the main treatments for mucormycosis, with proper surgical resection and correction of underlying predisposing conditions where feasible. In spite of technological advances, very high mortality rates persist in both IA and mucormycosis.

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