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Antimicrobial Original Research Paper

Invasive fungal infection in crtically ill patients: hurdles and next challenges

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A narrative review from a multidisciplinary task force of experts in critical care medicine and clinical mycology was carried out. The multi drug-resistant species *Candida auris* has emerged simultaneously on several continents, causing hospital outbreaks, especially in critically ill patients. Although there are not enough data to support the routine use of continuous antibiotic prophylaxis in patients subjected to extracorporeal membrane oxygenator, a clear increase of invasive fungal infection (IFI) has been described with the use of this device. Possible IFI treatment failures could be related with suboptimal antifungal concentrations despite dose adjustment. Invasive aspergillosis has become an important life-threating infection in intensive care unit related with new risk factors described. IFI remain important problem in critical patients due to the appearance of new risk factors, new species, and resistance increase. Multidisciplinary packages of measures designed to reduce IFI incidence and improve diagnostics tools may reduce the high mortality associated.

Keywords: ICU, Invasive fungal infections, Candidiasis, Aspergillosis, *Candida auris*, Challenges, Antifungal treatment

1. Introduction

In critically ill patients there are a number of clinical scenarios in which management and treatment are characterized by uncertainty. Despite the advances in research, diagnosis and the development of new molecules, invasive fungal infections (IFIs) represent one such scenario and constitute a challenge for intensivists, producing discrepancies and differences in patient management, and also serve as a stimulus for investigation. The intensive care unit (ICU) is the current hospital epicenter of many IFIs. As an example, the incidence of invasive candidiasis (IC) in the ICU is 7–10 times higher than in the hospital ward setting.[1] There are a number of reasons for this, including the admission of older patients with more comorbidities and with diseases and/or treatments involving new forms of immune suppression, the prolongation of survival under extreme conditions, the complexity of new surgical techniques, and multiple patient instrumentation.

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The genus *Aspergillus* acquires relevance in the respiratory infection of the critically ill patient in the last years and new risk factors for developing invasive aspergillosis have been described in this setting, such as steroid treatment and severe chronic obstructive pulmonary disease.[2]

A narrative review from a multidisciplinary task force of experts in critical care medicine and clinical mycology was carried out to describe the current situation of IFIs in the ICU (specially invasive candidiasis due to its major prevalence). In this first review the panel decides the main topics considering the new epidemiological situations and the therapeutic challenges in specific conditions that have changed in the last years, with special attention to those aspects that can help us to understand the current hurdles and future challenges facing us in these issues. The authors have selected neither diagnostic tools nor score of predictions. Antifungal agents have been ruled out of this manuscript. The purpose of this interdisciplinary team is to elaborate a new review periodically choosing the most relevant incoming troubles in this field.

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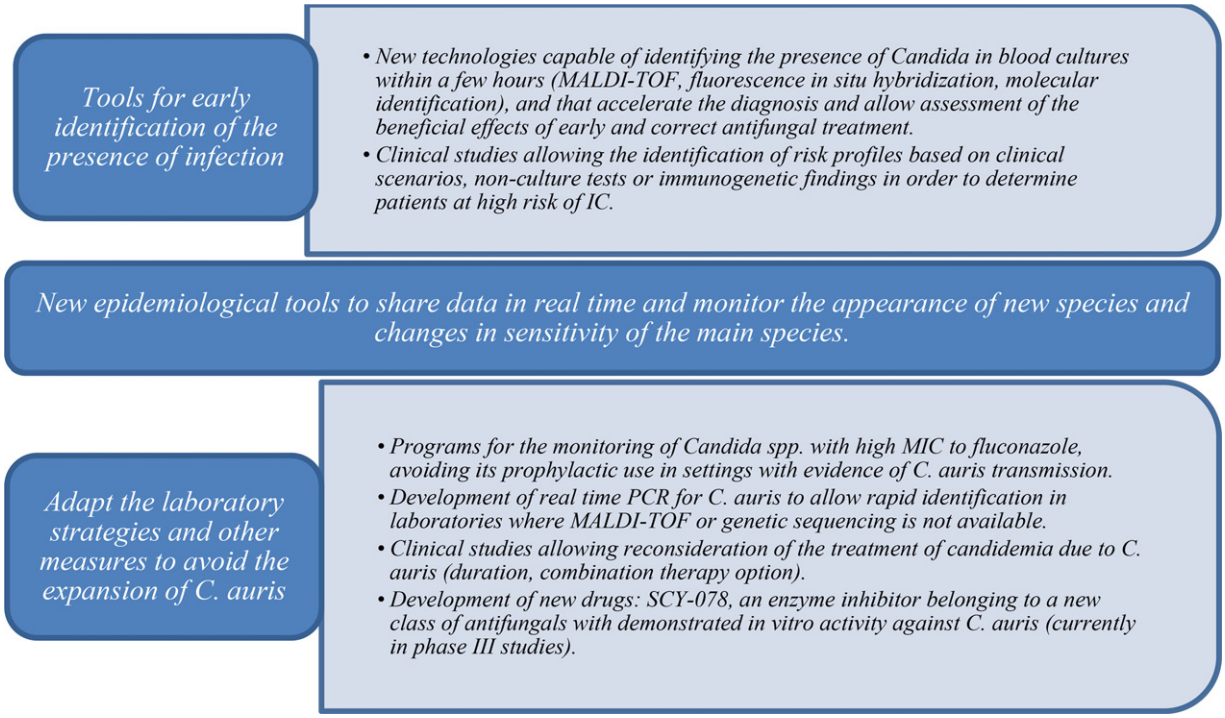
Table 1. Coming challenges in invasive candidiasis in critical patients.



2. The importance of new candida species: *Candida auris*

Candida auris was first isolated and identified in 2009 in the auditory canal of a Japanese patient and in recent years it has emerged simultaneously on several continents, causing invasive infections and hospital outbreaks.[3] The transmissibility of *C. auris* is far higher than that of other species and its identification proves difficult, since it cannot be made with the conventional techniques. Molecular studies have been published that confirm intra- or inter-hospital transmission.[4–6] Furthermore, molecular typification has shown isolates from the same areas to be closely related thus suggesting clonal spread, *C. auris* causes fungemia, as well as wound and ear infections, and is also isolated from urine, where it cannot be eliminated for up to months after infection.[7] The risk factors are analogous to those of other IFIs, with infection being more common in surgical patients, individuals with serious comorbidities and immune suppression, those who receive broad spectrum antibiotics, and patients with diabetes, kidney disease, HIV infection, solid tumors, and hematological malignancies.[4,7] Infection has also been described in newborn infants and associated to previous antifungal treatment in a significant number of patients.[8]

Although infections have been reported in different countries, the most relevant candidemia outbreaks attributable to this species have been described in the United Kingdom and Spain. An outbreak was reported in the cardiothoracic surgery department of a London hospital in 2016. Over a period of 16 months there were 50 cases of *C. auris* infection, and nine patients (18%) developed candidemia.[6] In Spain, an outbreak was documented in 2016 in the surgical ICU of a hospital in Valencia. Sixteen months after identification of the first case through sequencing, 250 colonized patients had been identified, with the recording of 64 candidemias – this representing 42% of all candidemia episodes recorded in intensive care, with a late complications rate of 37% and a mortality rate of 44%. An exhaustive study of over 100 healthcare workers failed to identify *C. auris*, though the study of environmental reservoirs proved repeatedly positive.[9] The adopted control measures included contact precautions, active yeast monitoring, skin decolonization with chlorhexidine, preventive isolation of patients with positive culture results, strict and rigorous control of both the environment and of the implicated staff, and echinocandin use as the main antifungal treatment.

The absence of *C. auris* in the databases of the laboratory kits can lead to incorrect identification, confusing the fungus with other species (*C. haemulonii, C. sake,* or other non-candida species). Furthermore, *C. auris* should be suspected when high resistance to fluconazole is confirmed in the

antifungal sensitivity tests. Correct identification of can be established by mass spectrometry (MALDI-TOF) or DNA sequencing techniques. When these techniques are not available, it is advisable to send non-albicans isolates with high fluconazole minimum inhibitory concentrations (MICs) to a mycology reference laboratory for definitive identification. This would be particularly important in the case of hospitals with a greater incidence of non-albicans species and for patients transferred from hospitals with outbreaks of *C. auris*. The United States Centers for Disease Control (CDC) also recommend monitoring the monthly number of blood cultures positive for non-albicans species, since any increment may be indicative of an outbreak.

Most isolates are resistant to fluconazole, though the sensitivity of the fungus to other azole drugs, amphotericin B and the echinocandins varies according to the isolate involved. A study involving 54 *C. auris* isolates found 50 to be resistant to fluconazole (93%), 19 to amphotericin B (35%), and four to echinocandins (7%). Overall, 22 were resistant to two or more classes of antifungals (41%) and two were resistant to three classes of antifungals.[8] The current recommendation is to prescribe echinocandins, with evaluation of the introduction of liposomal amphotericin B if fungemia persists.[10] Experts suggest combined treatment using both drugs, with the continuation of therapy for 3–4 weeks in the case of outbreaks.[9] The mortality rate associated to *C. auris* candidemia is subject to debate, due to the few published cases or descriptions of outbreaks, though the data suggest 30–40% even with antifungal treatment. Chowdhary et al. reported a global mortality rate of 33%, versus 57% in the case of ICU patients.[4]

Good infection control, including rigorous environmental cleaning measures, correct healthcare staff hygiene, adequate reprocessing of medical devices and adequate laboratory capacity, as well as patient isolation, are basic requirements for the prevention of transmission. The early identification of carriers with active surveillance cultures is a valuable tool for controlling outbreaks, together with rigorous environmental disinfection and cleaning measures. It is necessary to increase awareness in order to adopt laboratory strategies and implement improved control measures promptly enough to avoid new hospital outbreaks.

New diagnostic and epidemiological tools are needed to establish the appearance of new species and changes in sensitivity to antifungal drugs. The emergence of *C. auris* and the changes in ICU ecology make it necessary to modify the risk profiles, adapt the laboratories and investigate new forms of treatment. Table 1 summarizes the main challenges in the coming years.

4. Hurdles to overcome in IFIs

4.1. The role of antifungal resistance

A number of species are intrinsically resistant to antifungals (C. *krusei* to fluconazole and C. *lusitaniae* to amphotericin B), some are resistant to almost all available drugs (*Lomentospora prolificans* and *Fusarium solani*), and others present possible resistances to multiple drug substances (*C. auris*). An emerging problem, however, is the development of resistances to the current antifungals after exposure to such drugs. Examples are azole resistance in non-albicans species and in *Aspergillus fumigatus,* and resistance to echinocandins in the case of *C. glabrata*. Although the prevalence of such resistance is lower than with certain bacteria and antibiotics, the treatment options are very limited.

There are a number of underlying causes: permanent catheters; valve prostheses and invasive devices that can become colonized by biofilms impermeable to drugs; sites of infection where suboptimal drug concentrations are reached (peritoneum); poor adherence to therapy in chronic infections; antifungal prophylaxis; repeated treatment cycles or long-term therapies; exposure to agricultural fungicides that has seeded the environmental reservoirs with resistant organisms, etc. The Antimycotic Surveillance Program (ARTEMIS) reported an increase in *C. glabrata* as the cause of candidiasis from 18% (1992–2001) to 25% (2001–2007), with a parallel increase in resistance to fluconazole from 9–14% during the same periods.[11] In 2013, out of 1846 isolates from 31 countries, 11.9% of those corresponding to *C. glabrata* and 11.6% of the *C. tropicalis* isolates were found to be resistant to fluconazole.[12] Resistance to fluconazole can also imply resistance to other azole drugs, since the mechanisms that reduce susceptibility to fluconazole, such as point mutations in the ERG11 gene, also intervene in other azoles. The multicenter study published by Chen et al. reported resistance rates of 18.8% for fluconazole, 13.8% for itraconazole, and 10% for voriconazole.[13]

Current resistance to echinocandins is very low (about 3%), though *C. glabrata* may be an exception, with resistance rates of up to 10%.[12] Pfaller et al. identified 162 *C. glabrata* isolates resistant to fluconazole, of which 98% were resistant to voriconazole, 9.3% to anidulafungin, 9.3% to caspofungin, and 8% to micafungin.[14] Resistance is related to mutations of FKS (FKS1 for *Candida* spp increase and FKS2 for *C. glabrata)*, an increase has been observed in infections due to *C. glabrata*

in those centers where azoles are used and echinocandin prophylaxis is prescribed. Other clinical factors that promote echinocandin resistance include, host reservoirs including biofilms in the gastrointestinal tract, and intra-abdominal infections.[15] This suggests that a progressive rise in resistances can be expected (particularly to caspofungin, according to the published data), since an increasing number of hematological protocols contemplate echinocandin prophylaxis in the patient management algorithms.[16] Blanchard et al. have shown previous exposure to caspofungin to be an important risk factor for refractory fungemia.[17] In the SENTRY study, 11% of all candidemias resistant to fluconazole were also resistant to echinocandins.[12]

Van der Linden et al. in a multicenter study of 2941 *A. fumigatus* isolates, detected azole-resistant strains in 11 of the 19 participating countries, with a general prevalence of azole drug resistance of 3.2% that in turn was associated to a poorer prognosis (mortality rate 88–100% in the series).[18] In Spain, the very recently completed FILPOP2 study has reported 396 *Aspergillus* spp. isolates in 10 hospitals throughout the country, with the identification of three strictly azole-resistant *A. fumigatus* strains. This slow but progressive expansion in western countries must be taken into account and could open a new phase in the treatment of invasive pulmonary aspergillosis (IPA).

Resistance to antifungals is a threat to patient management and treatment success. A number of antifungals are currently being investigated, some with similar mechanisms of action and added advantages, while others are new compounds with mechanisms of action that overcome the resistance limitations and lessen the adverse effects.

4.2. The role of candida biofilm

The biomaterials used in prostheses, implants, endotracheal tubes, pacemakers, and different catheters offer surfaces that allow colonization and the formation of biofilms. However, such films can also develop on native tissues such as heart valves, the middle ear mucosa or alveoli; as a result, biofilms are believed to play a key role in about 70% of all subacute or chronic infections.[19,20]

A fungal biofilm is a heterogeneous community of microorganisms adhered to a surface and embedded within an extracellular matrix composed of polysaccharides, carbohydrates, proteins, nucleic acids, phosphates, and uric acid. These biofilms contain so-called quorum sensing molecules that diffuse within the film as communication signals. Two such quorum sensing molecules, tyrosol and farnesol, mutually counteract each other: tyrosol favors biofilm formation in the early and intermediate stages, while farnesol avoids excessive biofilm formation. Both are the target of new therapies that are currently in the investigational phase.[21] Their presence is essential for persistence of the infection and affords antifungal resistance, leading to the need to remove the biocompatible devices in order to eradicate the infection.

There are close interactions among the causal fungus (species and virulence factor), the host immune response (reduction of leukocyte microbicidal capacity or complement opsonization capacity) and the implant (material, surface, geometrical characteristics, roughness, electrical charge, and hydrophobicity) that influence development of the infection.

It is generally agreed that biofilms increase resistance to azole drugs and to a lesser degree to echinocandins and amphotericin B.[22,23] Differences have been observed with regard to the echinocandins and some studies have described greater antifungal activity with one drug type or other, depending on the fungal species involved.[24,25] New therapeutic strategies need to be defined: a) The combination of antifungals with different targets. The results to date have been discouraging, however. Tobudic et al. described a decrease in minimum inhibitory concentration (MIC) for posaconazole when combined with amphotericin B – an effect not seen when combining caspofungin with amphotericin B[26]; b) The combination of antifungals with antibacterial agents, particularly rifampicin or doxycycline with amphotericin B – with the description of positive results[27];c) The combination of antifungals with other drugs. In this regard, recent studies have shown simvastatin to be able to inhibit the formation of *C. albicans* biofilms.[28] One study found an alcoholic solution (ethanol) to quickly and completely eradicate a biofilm formed on a silicone catheter.[29] Stepanovic et al. in turn observed improvement on using high concentrations of acetylsalicylic acid[30] and Zhou et al. recorded improvements on combining it with amphotericin B in application to *C. albicans* and *C. parapsilosis* biofilms.[31] Other studies with ibuprofen and ambroxol have described a decrease in fungal activity[32,33]; d) The combination of antifungals with quorum sensing inhibitory molecules (farnesol); e) The combination of antifungals with cationic peptides; and f) The design and development of new biomaterials capable of preventing yeast adherence, such as for example ion and metal nanoparticle coatings possessing fungicidal activity; the use of drugs imbibed or immobilized on the biomaterial surface; or the use of polymers with antifungal activity.[34]

If allowed by the device and the patient clinical condition, it is essential to remove the causal device, with the need in some cases for surgery to remove the implant. The new therapeutic strategies may possibly include some of the abovementioned substances. However, the data available to date – though promising in some cases – are still insufficient and it seems clear that long-term effort will be required in this field.

Extracorporeal membrane oxygenation (ECMO) is an artificial and temporary respiratory and/or cardiovascular assist technique used in patients with refractory respiratory and/or heart failure. It has recently been introduced in the management of critical adult patients and its utilization will probably increase exponentially over the coming years.

The extracorporeal life support organization (ELSO) database compiles the information from 110–130 centers with ECMO programs. Bizarro et al. have recently reported the ECMO-related infections documented in 20,741 patients: a total of 2418 infections were observed, with a rate of 15 infections/1000 days of ECMO.[35] The most frequently isolated pathogens were coagulase-negative staphylococcus (15.9%), *Candida* spp. (12.7%), and *Pseudomonas aeruginosa* (10.5%).

However, these figures have raised controversy due to the possibility that many episodes classified as infections actually may have been colonization's. Schmidt et al. in 220 adults subjected to ECMO, reported 222 infections in 142 patients, with a rate of 75.5 infections/1000 days of ECMO, though there were only three candidemias among the 47 bloodstream infections diagnosed.[36] Kim et al. in turn described a series of 47 adults; of 13 patients with positive blood culture isolates, only two corresponded to candidemia (4% of the total patients).[37] Kim et al. in 61 adults, recorded 18 infections, with no cases of candidemia.[38] Sun et al. in 334 adults, documented 48 patients with blood culture isolates, of which seven corresponded to candidemia (2%).[39] Pieri et al. in an Italian series comprising 46 adults, recorded five candidemias (10.8%).[40] Lastly, Aubron et al. in an Australian retrospective study in 139 adults, documented 24 patients with bloodstream infections, of which nine were due to *Candida* (6.4%).[41]

There are not enough data to support the routine use of continuous antibiotic prophylaxis in patients subjected to ECMO, though such treatment involving a single dose or 24-h administration is advised when open or percutaneous cannulation is performed. Careful but aggressive antifungal prophylaxis is recommended in high risk patients (thoracotomy, prolonged antimicrobial use, and severe immune suppression), though such measures are not considered necessary in the rest of clinical scenarios. When antifungals are used, the same doses should be administered despite the possibility that lesser drug concentrations may be obtained when ECMO is used. Voriconazole should be avoided in all cases, due to its extensive membrane adsorption.[42,43] In view of the growing utilization of ECMO and its potential future applications, multidisciplinary programs designed to address these issues would be advisable.

4.3. Pharmacokinetic considerations

One of the reasons underlying possible treatment failure is the maintenance of suboptimal antifungal concentrations despite dose adjustment according to the summary of product characteristics. Recent studies doubt that the standard echinocandin doses are effective in all candidemias in the ICU. Martial et al. found the maintenance dose of micafungin (100 mg) to be sufficient for invasive candidiasis, though only 62% of the patients reached the pharmacokinetic target established for day three of treatment.[44] Suboptimum peritoneal concentrations have recently also been reported for some non-albicans species. In a micafungin population PK in plasma and peritoneal fluid in critically ill patients with proven or suspected intraabdominal fungal infection, it was observed very high PK variability, which corresponded to a relatively low PTA for less-susceptible pathogens.[45] Aguilar et al. in a series involving caspofungin, identified a subgroup of patients in which the pre-established pharmacokinetic targets were not reached.[46] Yagasaki et al. published a study in critical patients with renal replacement therapy and fluconazole treatment at three different doses: none of them reached optimum plasma levels. The authors therefore recommended an almost three-fold increase in the conventional dosage.[47] The few studies that have been published on liposomal amphotericin B and renal replacement therapy to date describe stable behavior, with no changes in the area under the curve (AUC) or modifications of the pharmacokinetic profile.[48]

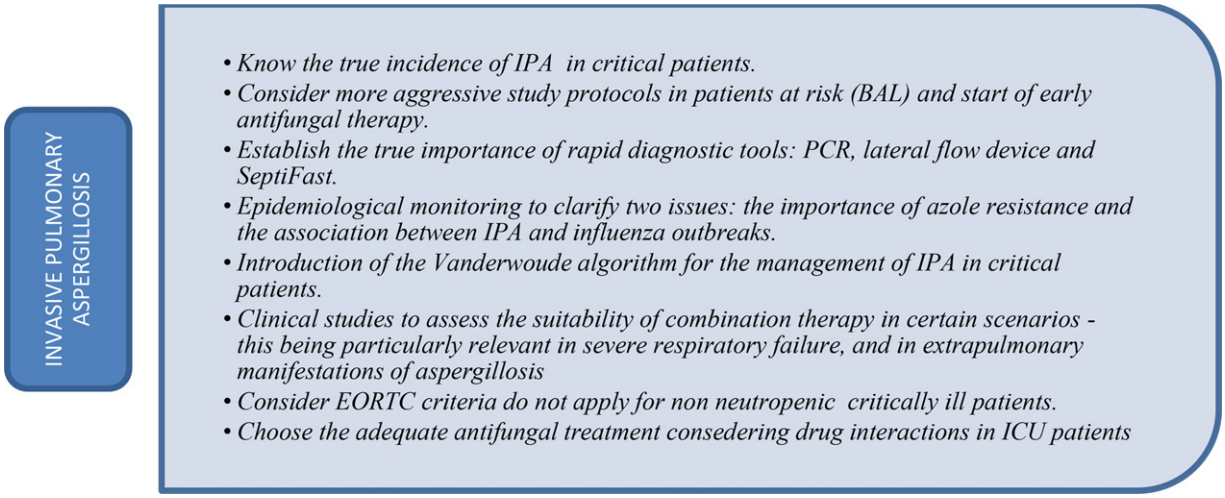
It now seems clearer that estimating patient exposure to a drug on the basis of the administered dose may sometimes not be enough. Fixed dosing of a drug can induce marked pharmacokinetic variability that cannot be explained only by fixed variables (age, height, race, or organ dysfunction), but which is also influenced by physiological changes associated to different stages of the disease. This is particularly evident in critical patients, where physio-pathological changes intervene (hydration, tissue perfusion, plasma proteins, and hemodynamic changes) that are

Table 2. Challenges in invasive candidiasis in the ICU for reducing mortality.

more patent in situations of hydrophilic drug prescription and the use of external agents that can further modify the drug concentrations (extracorporeal circuits, drug interactions, or vasopressor medication).

Drug monitoring is justified in certain situations characterized by unpredictable pharmacokinetic behavior, a narrow therapeutic margin, or defined concentration ranges. In general, the azoles (itraconazole, voriconazole, posaconazole, and isavuconazole) comply with these criteria. In contrast, the echinocandins and amphotericin B do not.[49] Drug interactions and certain clinical expressions of infection (associated to a poorer prognosis) reinforce the need to know drug levels. This is particularly relevant considering that different studies have revealed antifungal under dosing in critical patients – a situation that could result in increased mortality. At present, such monitoring faces a series of obstacles that pose a challenge for the intensivist. In many centers the response time is too slow in order for drug monitoring to be clinically useful. On the other hand, measurements of this kind require expensive equipment and highly qualified laboratory staff. In some cases, the monitoring of antifungals is centralized and this results in unacceptable delays. How to adjust the dosage when the latter is outside the desired range is not clear; although some authors suggest a 50% modification of the dose, there are no data to support such an affirmation. Software has been developed, allowing precise calculation of the regimen required to reach the new range (multiple model and BestDose) which could change the way in which treatment is administered in the ICU. However, among other requirements, such monitoring would

Table 3. Coming challenges in invasive pulmonary aspergillosis (IPA).



demand greater training and capacitation in clinical pharmacology.

Real time drug monitoring would be desirable, involving analytical values or infection markers. This idea has already been addressed with the use of galactomannan (GM) – not with diagnostic intent but for knowing the evolutive course of the disease, the response to treatment and, in some cases, the need for drug dose adjustment, without resorting to therapeutic ranges that have been constructed from patient populations instead of on an individualized basis. Persistently high GM values thus would indicate the need to increase the dose (independently of the concentration) and if this were not possible (due to toxicity), or if the rise in dose and concentration increment fails to result in normalization of the biomarker, a change in treatment or the addition of a second drug substance would have to be considered. Most of the fungal species produce a great variety of secondary metabolites that might be useful for monitoring the effect of the antifungal agent. While this approach remains to be validated in critical patients, it would constitute true individualized therapy.

The persistence of high mortality rates requires the adoption of new treatment strategies and new approaches to the management of resistances and infections associated to biofilms, adapted to the pharmacokinetic particularities of critical patients. The data available to date are promising in some cases, but are still insufficient; new challenges are therefore identified, as seen in Table 2.

4.4. Invasive aspergillosis

The isolation of *Aspergillus* spp. from respiratory samples in the ICU is relatively frequent. Contou et al. reported 423 critical patients with acute respiratory distress syndrome in which 8% yielded *Aspergillus* isolates.[50] The probability that such isolates imply infection is conditioned by many variables – one of them being the type of patient involved: 72% probability in neutropenic subjects; 55% in solid organ transplant recipients; and 22% in patients with chronic obstructive pulmonary disease.[51] The differentiation between infection and colonization in critical patients remains to be resolved, despite the availability of several algorithms. The instrument proposed by Vanderwoude is an old validated algorithm in critical patients, although can be used in the case of *Aspergillus* isolates from respiratory samples.[52]

Recently, a new attempt to improve this algorithm including host risk factors such as advanced stages of chronic obstructive pulmonary disease or liver cirrhosis, previous influenza, or identified genetic polymorphisms associated with an increased susceptibility to IFIs has been proposed by several authors.[53–56]

The risk factors have undergone changes in recent years and now individuals with chronic obstructive pulmonary disease, cirrhosis or severe liver failure are regarded as intermediate grade patients. Although the main risk factor is neutropenia and IPA has classically been related to allogeneic hematopoietic transplantation, currently only 10–15% of all critical patients with IPA have neutropenia and usually present other profiles: over 50% suffer chronic obstructive pulmonary disease and almost all receive corticosteroids.[57] Garnacho et al. in a multicenter study involving 1753 patients, found chronic obstructive pulmonary disease and corticosteroids to be associated to the isolation of *Aspergillus*.[58] A new risk group has been described very recently in a series of studies,

comprising patients infected with influenza H1N1. It has been postulated that the lymphopenia, immune alteration, and respiratory mucosal damage caused by the virus, even in immunocompetent individuals, predispose to the development of IPA; early fungal biomarker evaluation and imaging studies are recommended in these patients.[59]

The IPA mortality rate remains unacceptably high and is mainly determined by refractory respiratory failure. The AspICU study has recently reported one of the largest series of IPA in the ICU, comprising 563 patients, with mortality rates of 38, 67 and 79% in possible, probable and confirmed IPA. As predictive factors, the authors identified a higher SOFA score, patient age, bone marrow transplantation, mechanical ventilation, and the need for renal replacement therapy.[60] These mortality figures persist despite the novel biomarkers and cannot be explained only on the basis of drug resistance, for although resistance is an emerging problem, the proportion of patients infected with resistant *Aspergillus fumigatus* is low in our setting.

Table 3 describes the main challenges facing us in the coming years in the management of IPA in critical patients (modified from Basssetti et al.[61]).

5. Conclusion

Both invasive candidiasis and invasive aspergillosis remain important problems in critical patients, due to the appearance of new risk factors and new species, the growing use of new extracorporeal technologies and new devices, the increase in resistances, and the real need for new diagnostic techniques capable of serving as the new gold standards. More than the introduction of new drugs, we hope that the coming years will see the creation of multidisciplinary packages of measures designed to reduce incidence of fungal infections, improve diagnostics tools and reduce both morbidity and mortality of these patients.

Conflict of interest

No potential conflict of interest was reported by the authors.

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