Antifungal therapy in the ICU: how, when and whom?

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Introduction

Fungal infections in the intensive care unit (ICU) have become more prominent in adult and paediatric units, especially in surgical ICUs. The pathogens involved are mainly yeasts and moulds of Candida and Aspergillus. Candida species account for > 80% of all fungal isolates causing nosocomial infection whereas the rest are Aspergillus species, although fungal pathogens such as Fusarium and Rhizopus species are emerging [1]. Up to 10% of all blood stream infections are caused by Candida sp. which are responsible for 5-15% of all healthcare associated infections (HAIs), causing an elevation in the crude and attributable mortality from 20 to 70% and from 10 to 40%, respectively [2]. This Refresher Course lecture will focus on invasive Candida infection, and highlight the difficulties and controversies associated with diagnosis and treatment.

Candida fungaemia may result from endogenous (gastro-intestinal) or exogenous (for example, central venous line) sources. Episodes of candidaemia caused by Candida non-albicans species are being increasingly seen. In the ICU the problem is even greater, Candida infection is one of the most common bloodstream pathogens isolated after coagulase-negative Staphylococcus and Staphylococcus aureus. In a multicentre prospective study examining the risk factors for Candida bloodstream infections (CBSI) in surgical patients, the overall incidence of fungal infections was 0.98/1 000 patient days and this increased to 1.42/1 000 surgical ICU days when a central venous catheter was in place. Using multivariate analysis, factors independently associated with increased risk of CBSI included prior surgery (relative risk (RR) 7.3), acute renal failure (RR 4.2), parenteral nutrition (RR 3.6) and, in the case of surgical patients, the presence of a triple lumen catheter (RR 5.4) [3]. In a recent unpublished survey assessing the prevalence of peritonitis in surgical critical care units, Candida sp. were isolated from the peritoneal fluid of 12% of patients with peritonitis and, of these, 38% of the isolates contained non albicans species. Fungal infections affect not only mortality rates, but also morbidity, hospital stay and associated treatment costs.

Whom to treat?

The bug factor

Candida sp. are the most prevalent fungal infection, although other specific patient groups including immunosuppressed patients, such as those undergoing solid organ transplants or chemotherapy, may harbour other species. C. albicans is isolated in 50-70% of cases. The prevalence of other species is dependent on factors such as the geographical location, age, previous surgery and antifungal or antibiotic usage. For example, vancomycin and linezolid, have been associated with an an increased risk of C. glabrata or C. krusei infection [4].

Knowledge of local epidemiology is of vital importance. Moreover, the sensitivity of certain species to antifungal therapy is inconsistent. The usual sensitivity of C. albicans and C. tropicalis to a variety of antifungal agent does not occur with C. glabrata or C. krusei, which are becoming increasingly more resistant to all azoles. Sensitivity of C. parapsilosis to echinocandins can be variable. C. lusitaniae exhibits a diminished susceptibility to amphotericin B, whereas, conversely, C. guillermontii is sensitive almost only to amphotericin B.
When considering antifungal treatment, an attempt to identify which *Candida* sp. is most likely the likely pathogen seems to be a reasonable starting point and often fluconazole is used as the default treatment. Nevertheless, a multi-centre study has identified *C. albicans*, *C. tropicalis* and *C. parapsilosis* species previously considered fully sensitive to fluconazole, to be less susceptible to treatment with this drug. Multivariate analysis has identified several independent factors such as male sex (odds ratio (OR) 3.2), chronic lung disease (OR 2.7), presence of a central venous catheter (OR 4.0) and prior exposure to antifungal agents (OR 2.2) that are associated with reduced sensitivity to fluconazole. Prediction of sensitivity to fluconazole should be based on the identification of the species involved and consideration of other relevant factors that when combined may help assist in the choice of appropriate empirical anti-Candida therapy [5].

Of utmost importance is the fact that the cut-off limits for ‘in-vitro’ determination of sensitivity are set quite high by some clinicians and sometimes this cut-off limit could be set slightly differently in the ‘in-vivo’ scenario.

**The host factor**

Pamela Lipsett’s article asks ‘Can a normal person develop a fungal infection?’ [1]. She proceeds to mention Krause’s famous experiment [6]. Fungaemia and funguria can occur in a normal subject if exposed to a large inoculum of *Candida*. Recent experiments on mice have observed the effect of immunosuppressant drugs on the development of invasive candidiasis.

Loss of gastro-intestinal mucosal integrity is an essential prerequisite for *Candida* to gain access to the bloodstream via the gastrointestinal tract and the presence of immunosuppression alone is not enough. Host factors required to develop systemic candidiasis include proliferation of *Candida* in the gut (usually due to broad spectrum antibiotic exposure), mucosal barrier disruption secondary to trauma or chemotherapy-induced mucositis and the failure of the immune system with suppression of either T-cells (which usually prevent colonization and superficial invasion), epithelial cells, or reduced phagocytosis by macrophages and neutrophils (which usually prevent deep invasion and blood stream dissemination). Typically patients treated in the surgical ICU with candidiasis will be severely ill with multi-organ failure and septic shock often with post-surgical peritonitis [7]. This is the paradigm that defines the list of risk factors for invasive candidiasis (Table 1).

**Table 1**

<table>
<thead>
<tr>
<th>Independent risk factors for candidaemia in ICU patients</th>
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<tr>
<td>Prior abdominal surgery</td>
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<td>Intravascular catheters</td>
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<td>Acute renal failure</td>
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<td>Parenteral nutrition</td>
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<td>Broad-spectrum antibiotics</td>
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<tr>
<td>Prolonged ICU stay</td>
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<tr>
<td>Use of corticosteroids</td>
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<td>Colonization, particularly if multifocal</td>
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Identifying high-risk patients is the first step in reducing invasive fungal infection (IFI) related mortality [8]. The risk of invasive aspergillosis occurs in patients with acute myeloid leukaemia or myelodysplastic syndrome during remission or induction of chemotherapy or those undergoing allogeneic haematopoietic stem cell transplantation (HSCT), solid organ transplants (mainly lung transplantation) and patients with immunosuppression due to prolonged and severe illness. Establishing the actual risk of invasive candidiasis can be difficult. Epidemiological studies seeking to identify patients who would subsequently develop the condition prior to obtaining results from cultures has proved to be difficult in many of the cases studied. The risk factors for development of candidiasis may be classified as ‘internal’ (patient factors) and external (environmental factors). Internal risks that have a positive predictive value are renal failure, haematological...
malignancy, neutropenia, age < 1 month or > 65 years, and mucosal Candida sp. colonization. External risks include recent abdominal surgery, the presence of central venous catheters, administration of total parenteral nutrition or broad-spectrum antibiotics and a prolonged stay in the ICU.

Given the difficulty in diagnosing invasive candidiasis and the high mortality associated with this condition, identification of some of the risk factors and development of scoring systems have been used to assist diagnosis and aid treatment decisions [9]. One useful system, the ‘Candida Score’, includes factors such as parenteral nutrition, surgery, multifocal colonization and severe sepsis [10]. In summary this score allocates one point to the first three factors and two points to the last one, and, using a cut-off value of 2.5, this scoring system achieves an 81% sensitivity and 74% specificity for invasive Candida infection in non-neutropenic patients. Often such scoring systems and calculations based on statistical probabilities of risks are tools with low sensitivity, but they can provide a good negative predictive value to determine the likelihood of colonization and presence in surveillance cultures. Sometimes the ability to rule out infection in patients in whom antifungal treatment has already been started is as important as deciding to commence treatment in higher risk patients.

In ICU patients in whom many physical barriers are impaired, colonization also plays an important role in pathogenesis. Both duration and intensity of colonization are important. Pittet et al identified the intensity of Candida sp. colonization as an independent risk factor for subsequent invasive infection with genotypically identical Candida sp. strains [11]. They proposed both a colonization index and a corrected colonization index (the ratio of body sites positive for fungus on a given day (that is, the colonization index corrected for the density of fungal growth in the sample). The corrected colonization index had a > 66% positive predictive value for subsequent fungal infections. It is difficult to determine whether colonization precedes invasive infection or vice-versa. Is colonization a manifestation of incipient infection that is not yet clinically evident? Or are the pathogens present on the body surface the ones that will eventually invade? Some investigators have found colonization was present prior to obtaining positive blood cultures, whereas others have found the opposite. Moreover, the likelihood of confirming a positive culture in the presence of candidaemia is of the order of 50%. This raises an important clinical question: ‘Is it advisable to commence antifungal prophylaxis or empirical therapy in patients with multifocal fungal colonization?’

**Diagnostic tools**

Having identified a patient with the prerequisite risk factors displaying clinical signs of severe systemic infection in whom IFI is suspected, the first step should be to obtain appropriate samples (blood and other sterile fluids, etc) for culture prior to administering antifungal treatment.

*Candida sp.*

The diagnosis of invasive candidiasis is complex. From the clinical, radiological or pathological point of view, candidiasis does not display any unique characteristics to distinguish it from other infections. Confirmation by positive microbiological culture is still the gold standard; however, several days are needed to establish growth. Furthermore, fungi are common laboratory contaminants as well as being saprophytic human flora that can reduce culture specificity when trying to isolate the actual pathogenic organism. Consequently, awaiting positive cultures is not without its own problems.

IFIs manifest as very severe infections associated with a high morbidity and mortality especially in haematological oncology and surgical patients, as previously discussed. Waiting until a diagnosis is confirmed will usually delay initiation of antifungal treatment and may cause the clinical condition to become worse in the interim. Furthermore, even in the presence of candidaemia, positive cultures can be difficult to obtain (~ 50% of cultures even in the presence of a known candidaemia are negative to culture; this is actually no better than establishing a positive diagnosis than the toss of a coin!). The availability of quick and reliable diagnostic tests is therefore of major importance. This has stimulated interest in achieving a diagnosis without reliance on culture techniques. These diagnostic tests are based either on the identification of antigens or antibodies against antigens present in the cell wall or other parts of fungi, or on the identification the DNA from a particular fungi in tissue samples, so-called molecular models. These methods have been called the non-culture-based methods [12].
Immunological tests comprise mannan detection, a component of the Candida sp. wall and anti-mannan antibody detection, both of which are specific to Candida. The detection of (1-3)-beta-D-glucan (BDG) confirms the presence of another wall component of various fungi (Candida, Aspergillus and Pneumocystis) and is thus non-Candida specific. Furthermore, an antibody detection test against the germ-tube structure of Candida albicans (CAGTA) will identify growth in culture or invading host tissue. Perhaps the most widely used technique in recent years has been the Platelia Candida® (Bio-Rad), an ELISA test that detects both mannan antigens and antimannan antibodies in serum. With this test sensitivity reaches 80% and specificity 93%. The CAGTA – C. albicans IFA IgG® (Vircell) technique, developed in Spain, detects Candida albicans with a sensitivity of 84.4% and specificity of 94.7%, even in patients with negative blood cultures [13]. It has been observed that critical care patients with positive CAGTA antibodies have lower mortality rates; multivariate analysis has highlighted this positive result as the only protective factor to be independently associated with ICU mortality[14].

Detection of (1,3)-beta-D-Glucan (BDG), a panfungal wall component, is an alternative technique employed commercially by a system called Fungitell® (Cape Cod Incorporated). It is useful in the diagnosis of candidiasis in the critically ill. Sensitivities of 45-90% and specificities of 70-100% have been reported using this technique. Testing twice weekly is recommended. False positive test results can result from contaminated material such as surgical gauzes used during surgery which is the main disadvantage of this system. Mohr et al. evaluated the usefulness of BDG in a surgical ICU in trauma patients with clinical evidence of invasive candidiasis [15]. When using a positive cut-off of 80 pg/ml, they identified a 25% incidence of false positives when the first sample was taken on the third day of the patient’s ICU admission. Identification of invasive candidiasis using BDG demonstrated 87% sensitivity and 73% specificity when a clinical diagnosis of invasive candidiasis had been made. In patients with evidence of invasive candidiasis, the median BDG was significantly higher than those without it (171 vs. 48 pg/ml respectively). It appears that BDG detection may be a useful tool in the early diagnosis on invasive candidiasis in critically ill surgical patients, particularly after day 3 and in patients with at least two positive samples drawn several days apart. Moreover, there is a strong consensus that BDG testing has a very high (> 90%) negative predictive value which is valuable in order to withhold antifungal treatments where invasive candidiasis has been ruled out.

Molecular models that directly detect Candida specific DNA circulating in blood have been the subject of much research in the recent decades. The main problem has been the low fungal load, allied to the difficulty extracting and separating fungal DNA from human DNA. The first commercially available polymerase chain reaction method detects 25 micro-organisms in blood culture, including five species of Candida, as well as Aspergillus fumigatus (Septifast Roche, Penzberg, Germany). An increased sensitivity to the detection to C. albicans and C. glabrata has been reported but the true clinical significance of these findings has not been systematically assessed.

Other molecular methods applied to cultures in order to speed up the recognition of the different species of yeast are under development or just starting to be used clinically. One of these, the fluorescence in-situ hybridization test (PNA FISH AdvanDX, Woburn, Massachusetts, USA), differentiates the five most prevalent species of Candida [16]. An oligonucleotide array designed to identify Candida species has shown 100% accuracy, when compared with a conventional diagnosis based on positive blood culture positive for yeasts and fungi [12].

Aspergillus sp.

Conventional techniques used in the microbiological diagnosis of invasive aspergillosis (IA) are culture and morphological identification. Molecular identification of DNA segments has been increasingly used because morphological identification does not distinguish between some species, leading to an ongoing taxonomic revision of the genus Aspergillus.

An experimental revolution in the diagnosis of invasive aspergillosis (IA) has occurred in the last few years with the introduction of techniques such as galactomannan detection and development of high resolution diagnostic images. Both techniques form the basis for the EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group) definitions of invasive fungal disease [17].

In a recent meta-analysis the galactomannan test showed a sensitivity of 71% and a specificity of 89% for proven cases of IA, but subgroup analyses showed that the performance of the test differed by patient population and type of reference standard used [18]. This test has been validated mainly in haematological malignancy or in patients who have undergone haematopoietic cell transplantation rather than in solid-organ transplant recipients or immunocompromised patients. Nevertheless, galactomannan has been successfully used to detect IA in bronchoalveolar lavage in ICU patients without leukaemia or cancer. One study showed that whereas the sensitivity of galactomannan for IA was only 42% in serum, the sensitivity and specificity of galactomannan in broncho-alveolar lavage (BAL)
specimens was 88% and 87%, respectively. Thus it is recommended that BAL is conducted and a galactomannan test performed in every patient with a haematological malignancy or in ICU suspected of having IA.

Finally molecular techniques based on PCR, as described above, show a high sensitivity, clearly superior to any other diagnostic technique, however this theoretical superiority has not yet been proved in clinical practice.

How to treat?

Therapeutic tools

The treatment spectrum of fungal infections has been widened with the appearance of new antifungal molecules in the last few years. However, controversy has arisen in regard to the cost-benefit of these new treatments which include polyenes, azoles and echinocandins (Table 2).

Table 2
Drugs for treating fungal infections

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<th>Category</th>
<th>Drug(s)</th>
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<tr>
<td>Polyenes</td>
<td>Amphotericin B</td>
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<tr>
<td></td>
<td>Amphotericin B in lipid complex</td>
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<tr>
<td></td>
<td>Amphotericin B colloidal dispersion</td>
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<td></td>
<td>Amphotericin B liposome</td>
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<tr>
<td>Azoles</td>
<td>Imidazoles, nonsystemic: ketoconazol, miconazole</td>
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<td></td>
<td>Imidazoles, systemic: fluconazol, voriconazole, posaconazole, ravuconazole</td>
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<td></td>
<td>Triazoles: itraconazole</td>
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<tr>
<td>Echinocandins</td>
<td>Anidulafungin</td>
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<td></td>
<td>Caspofungin</td>
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<td>Micafungin</td>
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The selection of one or more of these drugs for treatment will be dependent on the fungus sensitivity, the clinical severity of the condition, local epidemiology and side-effects, and making a rational decision could be difficult for the inexperienced clinician. In the last few years guidelines have been reviewed and published in order to assist the selection process. Guidelines from the Infectious Diseases Society of America for the treatment of invasive aspergillosis and candidiasis are commonly consulted for this purpose [20, 21].

Following these guidelines, the treatment of the most common conditions, invasive aspergillosis and candidiasis is managed as follows.

Aspergillosis

For most of the invasive forms of aspergillosis from invasive pulmonary aspergillosis to Aspergillus peritonitis the primary recommended therapy is voriconazole (6 mg/kg iv every 12 h for 1 day, followed by 4 mg/kg iv every 12 h; oral dosage is 200 mg every 12 h), and as an alternative therapy amphotericin B, micafungin, posaconazole or itraconzole. For empirical and pre-emptive antifungal therapy (pre-emptive therapy is considered a logical extension of empirical antifungal therapy in defining a high-risk population with evidence of invasive fungal infection, for example pulmonary infiltrate or positive galactomannan assay result) the recommendation is liposomal amphotericin B (L-AmB) (3 mg/kg/day iv), caspofungin (70 mg day 1 and 50 mg/day iv thereafter), itraconazole (200 mg every day iv or 200 mg twice daily), voriconazole (6 mg/kg iv every 12 h for 1 day, followed by 3 mg/kg iv every 12 h; oral dosage is 200 mg every 12 h).

Candidiasis

Based on the IDSA recommendations [21] we will explain the treatment for candidaemia, as an example.
Candidaemia in non-neutropenic adults

Fluconazole 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily or an echinocandin (recommendation grade A-I). As alternative L-AmB 3-5 mg/kg daily; or Amphotericin B deoxycholate (AmB-d) 0.5-1 mg/kg daily; or voriconazole 400 mg (6 mg/kg) twice daily for two doses, then 200 mg (3 mg/kg) twice daily (A-I). The recommendation is to choose an echinocandin for moderately severe to severe illness and for patients with recent azole exposure. Transition to fluconazole is appropriate in many cases. Remove all intravascular catheters if possible (some authors do not endorse this recommendation). Treat for 14 days after first negative blood culture result and resolution of signs and symptoms associated with candidaemia. Ophthalmological examination is recommended for all patients.

Candidaemia in neutropenic patients

In this situation primary treatment would commence with an echinocandin or amphotericin lipid formulations (LFAmB 3-5 mg/kg daily (A-III). Alternatively fluconazole 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily; or voriconazole 400 mg (6 mg/kg) bid for two doses then 200 mg (3 mg/kg) twice daily (B-III).

However, some points deserve qualification. Generally urinary tract infections need only be treated if symptomatic. Central nervous system infection cannot be treated with an echinocandin. Infection within the cardiovascular system requires treatment with LFAmB with or without 5-flucitosyne as the option of first choice or an echinocandin (at higher doses than usual) as an alternative. The appearance of Candida sp. in respiratory tract specimens can always be regarded as a contaminant. Diagnosis of a respiratory tract infection requires confirmatory diagnosis with histopathological evidence. The appearance of Aspergillus sp. in blood cultures is also considered a contaminant.

New strategies based on the identification of new microbial targets and novel antimicrobial agents are the subject of ongoing research. An example of this research is the development of mycoviruses that are able to selectively infect fungi. Current knowledge of mycoviruses relevant to human pathogenic fungi and the scope for using (recombinant) mycoviruses as future biological control agents has been reviewed by van de Sande et al [22].

When to treat?

Although this could be regarded as the question that most needs answering, it is not easy to provide such an answer. The key conundrum is establishing the correct diagnosis and consequently there is no distinct division between the ‘when’ and ‘who’. The ability to establish the correct diagnosis accurately and quickly would be akin to finding the missing piece of the puzzle. What is obvious is that as soon as the results of cultures are available a specific treatment should be commenced. However, for all other patients at high risk of invasive fungal infection in whom there is no microbiologically proven diagnosis, we have a different strategy.

Antifungal prophylaxis

This treatment is given to patients in whom there is no clinical evidence of fungal infection, although they are at risk of developing it, before any signs, symptoms or microbiological results appear. Published evidence from meta-analysis supports the use of fluconazole as prophylaxis for liver transplantation such that the incidence of invasive fungal infection is reduced by ~ 50% [23]. However some authors have criticised this strategy arguing that only in high risk groups of patients where the incidence of invasive fungal infections is at least 10% and where the number needed to treat is equal to or less than 20, is antifungal prophylaxis worth initiating [24]. In other groups of ICU patients where the overall incidence is < 2%, prophylaxis should not be used. The high risk groups include patients with acute necrotising pancreatitis, recurrent gastro-intestinal perforations, and in solid-organ or allogeneic stem-cell transplantation. In some settings, where a prevalent burden of azole resistant Candida sp. exists, some authors recommend using a echinocandin as an antifungal prophylactic agent, arguing that this would reduce the selection of resistance and also contain costs. This recommendation is consistent with the IDSA guidelines which state that in environments with a high incidence of invasive candidiasis, antifungal prophylaxis in conjunction with a thorough review of infection control procedures may be a reasonable treatment strategy [21]. An argument against the use of antifungal prophylaxis in the ICU is the concern about the emergence of non-albicans Candida sp., about which there is no concensus at present.
Empirical antifungal treatment

This is the use of treatment in patients with clinical features consistent with a fungal aetiology or, alternatively, the initiation of treatment to patients without such features but in the setting of a very probable fungal infection, but without proven microbiological confirmation. This type of treatment is poorly supported in the literature, but is a very common strategy in clinical practice. It is based on the assumption that patients given antifungal treatment early would have a better outcome than when treatment is delayed pending microbiological confirmation.

Pre-emptive antifungal treatment

This is the initiation of treatment in response to a probable fungal infection, without microbiological confirmation (as in the case of the empirical treatment), but supported by the identification of one or more biological markers of infection risk.

For Candida sp., for example, these markers would include the risk score for the colonization index and the Candida score and biomarkers such as 1-3-β-D-glucan, mannan – antimannan antibodies, CAGTA or PCR techniques, together with high resolution imaging techniques or the galactomannan assay in the case of Aspergillus sp. With these some might consider colonization to be proven. The problem arises when subsequent infection needs to be diagnosed. In order to better establish the likely diagnosis of infection the use of biological markers such as C reactive protein or procalcitonin should be taken into account, even if they are not specific to fungal infection, they are of proven utility in the ICU setting. Perhaps molecular tests will eventually detect fungal DNA fragments more quickly and easily enabling the current thresholds determining use of pre-emptive rather than specific treatment to be refined. Until then, more studies are needed to shift from empirical to pre-emptive treatment thus ensuring that patients who do not have a fungal infection are not treated with antifungal drugs unnecessarily. This has the advantage of reducing both selective resistance to antifungals that are currently available, and, indeed, costs associated with their use.

Key learning points

• Use of antifungal drugs should be tailored to guidelines taking into account the susceptibility of particular fungi present in the locality and their prevalence. No antifungal drug is better than any another; they are simply different.
• A daily risk assessment for fungal infection should be added to ICU surveillance lists.
• There is little evidence to support use of antifungal prophylaxis except where the prevalence of fungal infection is known to be high (with a prevalence > 10%).
• Treatment of patients with fungal infections should be commenced as soon as possible. Consideration should be given to the possibility of fungal infection, taking into account all the relevant risk factors. Tests for biological markers and cultures should be requested. The distinction between specific pre-emptive and empirical treatment can sometimes be blurred by the severity of the condition.
• As well as those with haematological malignancies, other patients may require antifungal treatment. The incidence of invasive fungal infections is known to be increasing in the ICU setting. Here, the typical patient most susceptible to invasive fungal infections is the postoperative critically ill surgical patient with secondary peritonitis due to anastamotic leakage or the patient who has been subjected to long-term multiple broad-spectrum antibiotic treatment.
References