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REVIEW

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Epidemiology, diagnosis and treatment of systemic *Candida* infection in surgical patients under intensive care

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Abstract The incidence of systemic *Candida* infections in patients requiring intensive care has increased substantially in recent years as a result of a combination of factors. More patients with severe underlying disease or immunosuppression from anti-neoplastic or anti-rejection chemotherapy and at risk from fungal infection are now admitted to the ICU. Improvements in supportive medical and surgical care have led to many patients who would previously have died as a result of trauma or disease surviving to receive intensive care. Moreover, some therapeutic interventions used in the ICU, most notably broad-spectrum antibiotics and intravascular catheters, are also associated with increased risks of candidiasis. Systemic *Candida* infections are associated with a high morbidity and mortality, but remain difficult to diagnose and ICU staff need to be acutely aware of this often insidious pathogen. A number of studies have identified risk factors for systemic *Candida* infection which may be used to identify those at highest risk. Such patients may be potential candidates for early, presumptive therapy. Here we review the epidemiology, pathogenesis, morbidity and mortality of systemic *Candida* infections in the ICU setting, and examine predisposing risk factors. Antifungal treatment, including the use of amphotericin B, flucytosine and fluconazole, and the roles of early presumptive therapy and prophylaxis, is also reviewed.

Key words Intensive care unit · *Candida* · Fluconazole · Amphotericin B

Introduction

Candida species are increasingly important nosocomial pathogens. In the USA, the National Nosocomial Infections Surveillance (NNIS) program showed that the proportion of nosocomial infections caused by *Candida albicans* rose from 2% in 1980 to an average of 5% in 1986–89 [1]. Over the same period *Candida* spp. was the fourth most common pathogen isolated from ICU patients [2]. The NNIS also revealed that the rate of nosocomial fungal infections approximately doubled over the period 1980–90, the greatest increase occurring in surgical patients [3]. The increased incidence of nosocomial *Candida* infection in the surgical ICU is probably due to a number of factors. In recent years there have been changes in the patient population admitted to the ICU. The pool of patients receiving immunosuppressive anti-neoplastic or anti-rejection chemotherapy has grown, which increases the risk of *Candida* infections [4]. Improvements in supportive medical and surgical care have led to improved survival rates, creating a group of long-term ICU residents at risk of fungal infection. The use of broad-spectrum antibacterial agents appears to be particularly important. Their suppression of

Table 1 Most common pathogens in 2064 ICU-acquired infections in the EPIC study [8]

Pathogen	Incidence (% of ICU-acquired infections)
Enterobacteriaceae	34.4%
Staphylococcus aureus	30.1%
Pseudomonas aeruginosa	28.7%
Coagulase-negative staphylococci	19.1%
Fungi	17.1%

intestinal bacterial flora allows the proliferation of *Candida* within the gastrointestinal tract, which is a precondition of systemic infection [5].

The diagnosis of serious *Candida* infection may be difficult, although the clinical conditions which predispose patients to these infections are becoming better known and effective antifungal therapies are increasingly available.

Epidemiology

NNIS data showed that the incidence of primary *Candida* bloodstream infections increased by 487% in large teaching hospitals between 1980 and 1989. In smaller (less than 200 beds) hospitals, the increase was less dramatic but nonetheless substantial (219%) [6]. The overall rate of nosocomial fungal infections in hospitals participating in the NNIS program increased from 2.0 to 3.8 infections per 1000 patients discharged between 1980 and 1990. Among surgical patients, the incidence of all nosocomial fungal infections rose by 124%, the greatest of any patient group. In 1990, 16.1 fungal infections per 1,000 discharges were seen in burns and trauma patients, 10.1 per 1,000 in cardiac surgery patients, and 7.3 per 1,000 in general surgery patients; the vast majority (78%) of which were due to *Candida* species [3]. These surveys used standard CDC definitions of nosocomial infection, based on the isolation of organisms from sites of infection and specific clinical signs and symptoms according to the type of infection [7].

More recently, a study has been undertaken to determine the point-prevalence of nosocomial infections in ICVs in Europe. The European Prevalence of Infection in Intensive Care (EPIC) study collated data on 10,038 patients in 1,417 ICUs in 14 European countries on a single day in 1992. Of the patients, 44.8% were being treated for infection, of which 17.1% were associated with fungi. Fungi were the fifth most common pathogens, after Enterobacteriaceae, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and coagulase-negative staphylococci (Table 1). It is possible that the high rate of fungal infection observed in the EPIC study might, in many cases, have reflected misdiagnosis of fungal colonisation as infection. Nevertheless, over 50% of the patients in whom fungi were isolated were receiving antifungals, indicating that the attending physicians considered the isolates to be clinically significant [8].

Morbidity and mortality

In general, the impact of invasive *Candida* infections, in terms of morbidity and mortality, has not been studied in great detail, although *Candida* endophthalmitis is associated with a mortality rate estimated at 40–80% [9, 10]. Several studies have found crude mortality rates for candidemia in the range 25–60% [11–14], although these vary according to the study design and the population under investigation, and do not take into account other influential factors, such as age and underlying disease. One approach to determining the mortality attributable to candidemia is through the use of matched, case-controlled studies. One such investigation from a large teaching hospital found a mortality of 38% directly attributable to candidemia [12]. The cases included in this study all had nosocomial candidemia with records available and represented a large, varied population including a high proportion with neoplastic disease. In addition to mortality, candidemia was associated with considerable morbidity and a median hospital stay 8 days longer than that of controls. However, when only survivors were considered, the median length of stay was 30 days longer for cases compared to controls.

In the EPIC study, infections caused by fungi alone were associated with a 6% mortality. Mixed bacterial/fungal infections, although rare, were associated with a higher fatality rate, although the number of patients involved was small (Bruining H, unpublished data).

Pathogenesis of invasive *Candida* infections

Candida albicans is frequently present as part of the microflora of the gastrointestinal tract or the oropharynx in the normal human host. Alterations in host defence can lead to overgrowth of *C. albicans*. Hospitalisation, diabetes, thermal trauma and disease resulting in a compromised immune response are all associated with such colonisation [15–17]. The suppression of the normal bacterial flora in the gastrointestinal tract by broad spectrum antibiotic therapy also allows the yeast to proliferate. This may not produce systemic infection in otherwise healthy patients, but life-threatening illness may result in the critically ill [18, 19, 5]. Such *Candida* colonisation is probably a prerequisite for invasive infection; in neutropenic patients with hematologic malignancies, long-term and high density colonisation has been shown to lead to candidemia [20]. In non-neutropenic patients, candidemia is preceded by colonisation

or local infection with an identical strain [21, 22] and sequential spread of *Candida* colonisation from the abdominal cavity to other body sites prior to the development of candidemia has also been demonstrated [23, 24].

To cause an invasive infection, *Candida* usually penetrates mucosal barriers to gain access to the bloodstream. Many factors common to ICU patients, such as poor nutrition, trauma, hypotension, therapy with steroids or cyclosporine, and ischemia and reperfusion may damage the integrity of the gastrointestinal mucosa [25–30]. Abnormalities in the production of secretory IgA may also be involved in the translocation of pathogens across the mucosa [31]. When the integrity of the gastrointestinal mucosa is disrupted in the presence of *Candida* colonisation, penetration by the yeast in its hyphal form can occur, potentially leading to systemic infection [23]. Finally, some of the factors involved in disrupting the integrity of the gastrointestinal tract mucosa, such as nutritional status and ischemia, may also affect macrophage activity, thus influencing the clinical course of the infection [32].

Although it appears that most systemic infections with *Candida albicans* are caused by endogenous organisms via translocation from the gastrointestinal tract or by sequential spread from other body sites, apparent outbreaks of infection have been reported, raising the possibility of horizontal transmission. Most seem to have occurred in association with the use of parenteral nutrition in ICU patients [33–35]. The importance of horizontal transmission remains unclear, however: when strains available from two hospital outbreaks were analysed by DNA typing, no similarity was found between isolates from the same outbreak [36]. By contrast, restriction endonuclease analysis of DNA from isolates from one cluster of ten severe *Candida albicans* infections strongly suggested hand transmission as a mechanism of spread [37]. The presence of *Candida* on the hands of health care workers has been demonstrated; in one study an average of 39 % of surgical ICU staff were found to carry *Candida* species, suggesting that infection control measures may be valuable [38].

No-*albicans Candida* species are also an important cause of candidemia and disseminated candidiasis. The relative frequency of infections caused by these species seems to vary between institutions. In a study comparing fluconazole and amphotericin B in the treatment of candidemia in a population composed mainly of surgical ICU patients [39], non-*albicans Candida* accounted for 41 % of the cases. Some non-*albicans* species have also been associated with clusters of infections, including *C. parapsilosis* [40, 41]. *Candida glabrata,* [42] and *C. tropicalis* [43]. Unlike *C. albicans,* which is involved in a wide range of both community- and hospital-acquired infections and is well-documented as a commensal organism in healthy humans, some non-*albicans Candida,* such as *C. krusei* or *C. lusitaniae* are not generally found in the endogenous human microflora [4] and appear to be strictly nosocomial pathogens. Infection control measures may be of particular value against these species.

Definitions of *Candida* infections

The study of systemic candidiasis is complicated by inconsistencies in the literature and terminology used to describe various syndromes associated with *Candida* infection. The infections of most significance to ICU patients fall under the general heading of hematogenous candidiasis, a term that covers all *Candida* infections involving the bloodstream. Candidemia is defined as the isolation of any pathogenic species of *Candida* from at least one blood culture specimen. The term disseminated candidiasis refers to *Candida* infection in multiple non-contiguous organs and implies hematogenous spread of the pathogen. Chronic disseminated candidiasis, also known as hepatosplenic candidiasis, has only been described in patients who have experienced prolonged severe neutropenia, and not in non-neutropenic surgical patients.

Disseminated candidiasis, involving the formation of micro-abscesses in multiple tissues and organs, is a difficult infection to eradicate, even in the immunocompetent host, and therapy is aimed at resolving candidemia before disseminated infection becomes established.

Problems in diagnosis

The diagnosis of systemic *Candida* infection is problematic, as the clinical presentation is variable and nonspecific. Fever occurs in up to 80 % of cases and leukocytosis in up to 50 % [44]. Patients with *Candida* infections may not immediately appear to be seriously ill, or may present with septic shock [23]. In the absence of definitive clinical findings indicative of candidiasis, such as Candida endophthalmitis or tissue histology, diagnosis is largely based on the presence of *Candida* in blood samples.

Although candidemia is generally used as an indicator of the need to begin antifungal therapy, its true significance remains unclear. Candidemia is associated with considerable mortality [12], but systemic infections can occur when blood cultures are negative. The bloodstream is probably the route of dissemination of *Candida* from the gastrointestinal tract. Candidemia is probably best regarded as a marker of hematogenous spread of *Candida,* and patients with candidemia may or may not already have disseminated infection. Established disseminated candidiasis is more difficult to diagnose; the most common manifestation being endophthalmitis. Ophthalmologic examination is a valuable tool for mon-

Table 2 Risk factors for candidemia and disseminated candidiasis

Neutropenia*	Multiple blood transfusion
Long-term use of central venous catheters*	Hemodialysis*
Candida colonisation*	Diabetes mellitus
Broad-spectrum antibiotics*	Corticosteroids
Length of stay in ICU	Immunosuppressants
Venous catheters	Parenteral alimentation
Mechanical ventilation	Urinary catheter

* Independent risk factors for disseminated candidiasis by multiple logistic regression analysis

itoring patients at risk of disseminated candidiasis and can establish infection in patients with negative blood cultures and no detectable colonisation at other sites. *Candida* endophthalmitis is a relatively rare condition however, being found in 9–15 % of candidemic patients [39, 45]. Other manifestations of disseminated infection are even less common, skin lesions and septic arthritis being rare in ICU patients [4]. High-grade candiduria in patients who have not undergone procedures involving the renal pelvis or bladder and who do not have indwelling urinary catheters is strongly suggestive of renal infection of hematogenous origin [23].

Given the high mortality attributable to candidemia, a single positive culture should not be regarded as representing benign, transient colonisation. The detection of *Candida* at other usually sterile sites, such as ascitic fluid or CSF, should also be considered adequate justification to begin therapy. At the present time, serological and molecular techniques for the detection of *Candida* are under development, but to date their clinical utility is unproven [44, 46].

Risk factors for systemic candidiasis

Because of the non-specific presentation of systemic *Candida* infections, it would be useful to identify patients who are at high risk of candidiasis in order to initiate antifungal therapy. A variety of recognised high-risk groups, such as neutropenic cancer patients and recipients of bone marrow or solid organ transplants, are increasingly found in the ICU. Outside these very high-risk groups it is possible, however, to identify specific risk factors which predispose ICU patients to systemic *Candida* infection (Table 2).

Colonisation with *Candida*

The spread of *Candida* from the abdominal cavity to other body sites prior to invasion of the bloodstream was first demonstrated in the early 1980s [23]. Candidemia is frequently preceded by colonisation of infection with a genotypically identical strain of *Candida* [21]. Several studies in various patient populations have demonstrated the importance of *Candida* colonisation as a risk factor for subsequent systemic infection. In a matched case-control study by Wey et al. [47], which considered all cases of nosocomial candidemia in a tertiary care hospital, multiple logistic regression analysis revealed that colonisation at sites other than the blood was one of four independent risk factors for candidemia. Martino et al. [48], in a study of cancer patients, found that candidemia occurred in 32 % of patients with colonisation at multiple sites, compared with 1 % of patients with single site and 0.5 % of those not colonised with *Candida*. A subsequent study by the same authors, with larger patient numbers, confirmed these findings. Twenty-two percent of patients with multiple-site colonisation developed candidemia, compared with 5 % of those with single site, and no candidemia in patients without prior colonisation [49]. In cancer patients, a multivariate logistic model showed that peripheral cultures positive for *Candida* were a significant risk factor for candidemia [50].

A cohort of critically ill surgical patients has been prospectively followed in an attempt to determine the role of colonisation in the development of invasive infection [24]. The study population comprised patients in whom microbiological surveillance cultures from various body sites had revealed significant *Candida* colonisation; 29 patients were thus identified. Eleven subsequently developed severe invasive *Candida* infections, whereas the remaining 18 did not. Analysis of the factors distinguishing the two groups revealed intensity of colonisation, quantified as the ratio of the number of non-blood body sites colonised by *Candida* compared with the number of sites sampled, to be significantly higher in patients who subsequently became infected than in those who did not. Inclusion of the density of fungal growth heightened the significance of this finding. This observations was echoed in a study of low birth weight infants, which found a positive correlation between colonisation density, the presence of gastrointestinal symptoms and candidemia [51]. A high concentration of *Candida* in the stool has also been shown to be a significant risk factor for candidemia in adult cancer patients [20]. The duration of exposure to broad-spectrum antibiotics was not statistically significant in this study.

Severity of underlying illness

One factor which appears to have a major influence on the probability of developing systemic *Candida* infection in the ICU is the severity of the patient's underlying condition. The APACHE II severity score has emerged as an apparent risk factor from three studies [8, 24, 52]. However, APACHE II score as a predictor of infection

is a circular notion: APACHE II measures fever, hypotension and other parameters of infection. The fact that infected patients have higher APACHE scores than non-infected patients therefore reflects the descriptive, but not predictive, value of the system.

Length of ICU stay was found to be a significant risk factor in univariate analysis in the Wey study [47], but not in multiple logistic regression analysis. In this study, however, cases and controls were matched for underlying disease. The EPIC study also found length of ICU stay to be associated with an increased risk of infection [8]. In the study by Pittet et al. [24], one of the entry criteria was an ICU stay of longer than 10 days; 11 of the 29 patients in the study subsequently developed candidemia.

Antibiotics

If systemic candidal infections occur through excessive growth of *Candida* in the digestive tract followed by penetration of the mucosa leading to hematogenous dissemination, prior use of antibiotics would be a risk factor for the development of *Candida* infection to the extent that they cause disturbance of the normal gastrointestinal flora and overgrowth of *Candida* species.

The use of antibiotics emerges as a risk factor in all studies of the epidemiology of candidemia. The number of antibiotics used was the strongest predictive factor for candidemia in the study of Wey et al. [47], but there was substantial overlap between the infected and non-infected groups. In a second study [24], the duration of prior antibiotic therapy was one of three factors that differentiated infected from uninfected patients, but was not significant by logistic regression. In a third study [52], extensive antibiotic usage was significant in that 94% of the candidemic patients had received antibiotics, and 62% at least four, prior to developing candidemia.

Different broad-spectrum antibiotics may vary in their ability to predispose patients to *Candida* overgrowth. Studies of their effect on human gastrointestinal flora have shown that increases in the yeast population in the intestine are related to decreased numbers of anaerobes recovered from stool samples after treatment [53]. There is some evidence that treatment with cephalosporins, in particular ceftriaxone, is more likely to lead to candidal overgrowth than the use of aminoglycosides or imipenem [54–56].

Factors associated with ICU care

In the ICU, patients are subjected to a number of therapeutic and supportive interventions which interfere with the normal barriers to the entry of micro-organisms or with mechanisms for clearing them. Examples include mechanical ventilation and intravascular catheters. Multiple logistic regression analysis has identified the use of Hickman catheters as an independent predictor of *Candida* infection [47], and univariate analysis showed that the use of Swan-Ganz catheters, parenteral nutrition, multiple blood transfusions and artificial ventilatory support were also significant risk factors. Not all of these risk factors, however, are confined to the general ICU population, as Hickman catheters, for example, are seldom used in this setting. Central venous catheters also emerged as a significant risk factor in cancer patients in a study by Karabinis et al. [50]. In the EPIC study [8], several factors appeared to be associated with subsequent fungal infection, including the use of central venous catheters, assisted ventilation, duration of ventilation and tracheostomy, although the latter may simply be a reflection of the duration of ventilation.

Specific therapeutic interventions may actually reflect the severity of the patient's underlying condition, and therefore serve only as secondary, dependent risk factors. That systemic candidiasis appears to be a phenomenon predominantly associated with endogenous pathogens would tend to support this view, as vascular catheters, for example, would not represent a portal of entry for *Candida*.

Treatment of candidemia and disseminated candidiasis

In the past, many patients with candidemia were left untreated. In some centers it was the practice to decide whether or not to treat according to the clinician's perception of the patient's risk of having disseminated candidiasis. Treatment was not given to patients thought to have a relatively low probability of systemic infection. The rationale behind this strategy was the belief, based on two studies, [57, 58] that *Candida* was not a significant pathogen and that candidemia was a benign, transient event. The toxicity associated with amphotericin B, the only available systemic antifungal agent at that time, was considered to be so severe that therapy was often reserved for patients who obviously had systemic infection. This strategy, however, has become outmoded. The high incidence of long-term sequelae associated with this approach, the recognition of the high mortality attributable to candidemia [12, 52] and the difficulty of predicting which patients have or will develop disseminated candidiasis if untreated, coupled with the availability of less toxic systemic antifungals, such as fluconazole, have led to a consensus that all cases of candidemia should be treated [59].

Amphotericin B

Amphotericin B has been in clinical use for the treatment of systemic fungal infections for over 30 years. This polyene compound has a very broad antifungal

spectrum, including most species of *Candida,* although it is not active against C. lusitaniae [60]. Dosage recommendations for candidemia were initially based upon doses employed for histoplasmosis, 1 mg/kg per day. More recent work has demonstrated the efficacy of lower dose regimens of 0.3–0.7 mg/kg per day, with treatment courses of 7–10 days [61, 62]. Amphotericin B toxicity predominantly consists of fever, chills, nausea, vomiting, hypotension and, most importantly, renal tubular damage. Almost all patients receiving amphotericin B develop nephrotoxicity to some extent [60]. The toxicity associated with amphotericin B can be minimised by the careful management of therapy. Nephrotoxicity, for example, can be reduced by sodium loading (i.v. administration of 500 ml normal saline) prior to administration, or by administering pentoxyfylline. Amphotericin B is used in many centers to treat hemodynamically unstable patients. The use of amphotericin B has been reviewed elsewhere [63].

In the early 1980s, amphotericin B was incorporated into liposomes, in an attempt to increase its therapeutic index. Initial investigations with liposomal formulations in neutropenic mice confirmed that a significant reduction in toxicity could be achieved without loss of efficacy [64]. Later clinical studies confirmed that the liposomal product had significantly less nephrotoxicity than conventional amphotericin B [65]. Three lipid formulations of amphotericin B have been developed, and are licensed for clinical use in Western Europe. The toxicology, pharmacokinetics, and antifungal properties are different for each. Because these formulations are better tolerated than standard amphotericin B, larger dosages can be prescribed. However, when equivalent doses are compared with standard amphotericin, the concentrations in serum are lower with the lipid preparations, which may be a consequence of accumulation in the liver and the spleen. Potential problems to consider with the use of the new ampholiposomes in critically ill patients have been reviewed recently in detail [66].

Despite evidence of decreased nephrotoxicity and possible increased therapeutic index, liposomal formulations of amphotericin B have not been found to be associated with enhanced efficacy in clinical conditions. There is no controlled trial comparing those formulations with standard amphotericin B, and further data must accumulate before recognising the possible therapeutic advantage of ampholiposomal forms in clinical practice. Finally, it is worth noting that those preparations are 10- to 50-fold more expensive than the standard formation. Despite their established efficacy in treating invasive candidiasis and severe systemic mycoses, there remains limited clinical experience of these drugs in the ICU setting. Thus, at present, their use is not recommended in those patients.

Fluconazole

The triazole antifungal fluconazole is increasingly used in the treatment of candidemia. Like other azole antifungals, it blocks sterol biosynthesis by inhibiting fungal cytochrome P450 enzymes. An earlier azole antifungal, ketoconazole, is effective against yeast infections of the skin and mucous membranes, but should not be used to treat hematogenous candidiasis. Ketoconazole is not available in intravenous form, and its oral bioavailability is erratic and dependent on gastric acidity. Fluconazole, by contrast, has high oral bioavailability which is not dependent on gastric acidity, is also available for intravenous administration and is distributed evenly in body tissues [46].

Fluconazole and amphotericin B have been compared in the treatment of candidemia, although patients with neutropenia, hematologic malignancies or AIDS, organ transplant recipients and burns were excluded [39]. The study population was made up largely of surgical patients. Fluconazole and amphotericin B were not significantly different in the treatment of candidemia in terms of outcome: 79% of patients on amphotericin B had successful outcomes, as did 72% of those receiving fluconazole ($p = 0.22$). In a secondary analysis, including only those who had received antifungal treatment for at least 5 days, amphotericin B was associated with an apparently higher success rate than fluconazole (86% versus 75%, $p = 0.05$). However, this difference was not due to persistent candidemia, toxicity or deaths, but rather to therapeutic modifications late in the course of treatment or after it had been completed (Table 3). For example, patients who required systemic antifungal therapy for more than 4 days for asymptomatic *Candida* urinary tract infections after the end of primary therapy were scored as relapses, irrespective of the outcome of primary treatment. This occurred in three patients in the fluconazole group and one who received amphotericin B. When these four technical failures were re-scored as successes, the between-group difference was no longer statistically significant. Furthermore, the scoring system did not require survival beyond the end of therapy for a patient to be considered a success. When a second post-hoc analysis was performed, requiring survival for 7 or 14 days after the end of therapy for success, the outcome was virtually identical for the two drugs. Fluconazole had a significantly lower incidence of hypokalemia and elevations in blood urea nitrogen and serum creatinine.

Other large comparative studies [67, 68] have found no significant differences between fluconazole and amphotericin B in efficacy, but showed the former was significantly better tolerated. Fluconazole has also been shown to be effective in the treatment of chronic disseminated candidiasis [69, 70].

Table 3 Reasons for treatment failure and relapse in a comparative study of amphotericin B and fluconazole [39]

Cause	Treatment group	
	Amphotericin B ($n = 103$)	Fluconazole ($n = 103$)
Failure at end of therapy		
Blood cultures remained positive	12	15
Toxic effects	3*	2
Persistent/recurrent fever with negative cultures	–	4
Saccharomyces cerevisiae fungemia	–	1
Abdominal abscess persistently culture positive	–	2
Withdrawal from study after ≤ 4 days without definite improvement or failure	4	3
Relapse		
Late discovery of *Candida* abscess	1	1
Hypotension with negative cultures treated with systemic antifungals	2	–
Asymptomatic funguria treated with systemic antifungals	1	3

* One patient receiving amphotericin B had both toxicity and persistent *C. albicans* fungemia. This patient is included under both headings

In cases where *Candida albicans* is the infecting pathogen, fluconazole is the preferred therapy, in view of its lower toxicity. Fluconazole is also available in an oral dosage form, which enables patients to take it by mouth when possible, an approach that may be useful in patients with endophthalmitis, for example, where therapy must be continued until at least 10 days after the ocular lesions have resolved [46]. Some *Candida* species are poorly susceptible to fluconazole, most notably *C. krusei.* Many strains of *Candida glabrata* are also less susceptible to fluconazole than *C. albicanis.* Where these species are isolated from patients, or where they are particularly common, amphotericin B may be the preferred antifungal agent.

Dosing recommendations for fluconazole vary between countries and institutions. In Europe, 400 mg/day is the usual dosage, and therapy is continued for 10–14 days in cases of candidemia. In Japan, 400 mg/day is reserved for hemodynamically unstable patients, 100–200 mg/day being the usual regimen. In the USA, although 400 mg/day is the maximum permitted by the FDA, higher doses are being used in clinical trials and debate is currently centered on whether an 800 mg dose should be used routinely. We recommend that fluconazole should be started at a dosage of 600–800 mg/day, given intravenously for 3 days, followed by 400 mg/day given either orally or intravenously if the patient is well enough.

Combination therapy

In some centers, amphotericin B is used in combination with fluconazole, particularly in critically ill patients with septic shock or in transplant recipients. This approach allows the duration of amphotericin B treatment to be kept to a minimum, reducing the chances of significant toxicity. However, there have been some concerns of an antagonistic effect between amphotericin B and the azoles. Consequently, until the combination has been formally evaluated in clinical trials, it should be used with caution.

Although flucytosine is no longer available in some countries, and its use as monotherapy for systemic candidiasis is associated with a high failure rate and the emergence of resistance, it remains a useful compound in combination with amphotericin B, and there has also been the suggestion that it may be usefully combined with fluconazole [46]. Combination with flucytosine can extend the antifungal spectrum of both compounds. Nevertheless, the use of a flucytosine/amphotericin B combination is potentially problematic. Flucytosine is associated with granulocytopenia and gastrointestinal toxicity, and is excreted almost entirely by the kidney. In patients with nephrotoxicity associated with amphotericin B, the reduced clearance of flucytosine can result in toxic drug levels. It is worth noting, however, that the current recommended dosages of flucytosine (typically 37.5 mg/kg every 6 h) may be too high for the treatment of *Candida* infections. These dosages are based on those needed to achieve penetration into the CSF in cryptococcal meningitis. Flucytosine 25 mg/kg per day administered at 12-h intervals should be adequate to maintain serum levels above the MICs for most susceptible *Candida* species [46]. Flucytosine serum levels should be monitored during therapy [71]; this is of particular importance when this compound is used in combination with amphotericin B.

Early presumptive therapy

Deciding when to initiate antifungal therapy is often troublesome, because of the difficulty of detecting disseminated *Candida* infection. Those patients who are candidemic require therapy, but some patients with system-

Table 4 Indications for empiric antifungal therapy, British Society for Antimicrobial Chemotherapy working party recommendations [71]

Clinically unstable premature neonate with candiduria or *Candida* colonized skin break
Candiduria in a high-risk patient with deteriorating clinical status
Single *Candida*-positive blood culture in an at-risk patient
Isolation of *Candida* from any sterile body site (except urine)
Positive microscopy for yeast from a sterile specimen
Histologic evidence of yeast or mycelial forms in tissue from at-risk patients

ic infection may have blood cultures that are consistently negative. Given the high mortality associated with candidemia, early presumptive antifungal therapy should be considered in patients who are at high risk of *Candida* infection [46]. The use of fluconazole as early presumptive therapy in ICU patients is an area in which well-designed clinical studies are urgently required. In the absence of such studies, we do not wait for positive blood cultures in a patient with suspected severe *Candida* infection. Using information obtained from the clinical condition of the patient, the presence of risk factors for *Candida* infection and the intensity of the *Candida* colonization, the odds for infection can be estimated and treatment started accordingly [46].

Although no data from controlled clinical studies on early presumptive therapy are available, the British Society for Antimicrobial Chemotherapy (BSAC) working party recently published recommendations for the management of deep *Candida* infections in surgical and ICU patients. Their report suggests that presumptive therapy might be useful in patients at particularly high risk. Patients in this category include those recovering from gastrointestinal surgery or suffering from pancreatitis who have several risk factors for infection. The BSAC working party also proposed a number of other clear indications for the initiation of antifungal therapy (Table 4) [71]. In addition, algorithms for the management of patients at risk of *Candida* infection have recently been proposed based on risk factors for infection, the presence of *Candida* colonization, the clinical condition of the patient and the efficacy of antifungals [46, 72].

Antifungal prophylaxis

Systemic antifungal prophylaxis is not recommended in the general surgical ICU population. Some centers use prophylaxis in liver transplant recipients. Fluconazole or oral amphotericin B is added to the SDD regimens used prior to surgery. Amphotericin B at the usual dosage carries a high risk of toxicity which precludes prophylactic use in these patients, but studies have evaluated low-dose amphotericin B [73, 74] or liposomal forms of the drug, the latter in bone marrow transplantation [75]. To date, no formal studies of fluconazole as antifungal prophylaxis in organ transplant recipients have been performed, although a retrospective review of patients receiving liver transplants for fulminant hepatic failure at one center in the UK has been reported. Prior to the introduction of fluconazole prophylaxis, eight deaths due to fungal infection occurred in 72 patients (11.1%), six of which were due to *C. albicans* (8.3%), whereas in 45 patients who received fluconazole prophylaxis (100 mg/day), no deaths due to invasive *Candida* infections occurred, and there were three deaths (6.7%) attributable to fungal infection (*Aspergillus* and *Mucor* spp). No invasive *C. albicans* infections were observed in patients receiving fluconazole prophylaxis [76]. Trials in bone marrow transplant recipients and neutropenic cancer patients have shown fluconazole to be effective and well tolerated in these patient groups [77–81]. The role of antifungal prophylaxis in both organ transplant recipients and the general surgical population remains to be defined, however, and is another area in which well-conducted studies would be valuable. It seems likely that the role of prophylaxis will become more clearly defined as our understanding of the risk factors for systemic *Candida* infections increases.

Conclusion

Although considerable progress has been made in recent years in understanding the pathogenic role of *Candida* in ICU patients and in the management of such infections, many questions remain to be answered. The increasing incidence of systemic *Candida* infection in this patient population, coupled with the high associated morbidity and mortality, is a clear indicator of the need for those involved in ICU care to be acutely aware of this pathogen.

In the light of this, there is a clear need for further research into a variety of aspects of the management of candidemia and disseminated candidiasis. The difficulty of diagnosis of disseminated candidiasis means that the emphasis should be placed on the identification of patients at high risk of infection and the use of early presumptive therapy. A number of studies have identified potential risk factors for candidemia and further work in this area, perhaps involving larger patient numbers and more specifically targeted at the general ICU population, should make it possible to validate these factors. In turn, this will greatly simplify the definition of an at-risk population.

The development of fluconazole has made both antifungal prophylaxis and early presumptive therapy for

patients suspected of having candidemia or disseminated candidiasis more attractive. These are areas where further studies are urgently needed; the role of antifungal prophylaxis in the ICU patient remains to be defined and the establishment of effective methods of presumptive therapy, combined with a deeper understanding of the risk factors, would probably improve the survival of patients at risk of systemic candidiasis.

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