Management of candidiasis in the intensive care unit

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In the last two decades, Candida has emerged as an important opportunistic pathogen. Patients admitted to the intensive care unit (ICU) are particularly susceptible to this infection because of the severity of their underlying illness and the excess use of medical and surgical interventions. The frequent use of antibiotics, central venous catheters and other intravascular devices as well as poor gut motility or abdominal surgery place these patients at high risk of infection, which contributes to the morbidity and mortality of the already critically ill patient. Early recognition and appropriate management of invasive candidiasis are therefore important. This article addresses important management issues such as the role of screening for Candida colonization, the use of prophylaxis and the choice of antifungal agents for the treatment of presumed and proven invasive candidiasis in the adult ICU setting.

Keywords: ICUs, treatment, prophylaxis

Introduction

Nosocomial Candida infections such as candidaemia have emerged as an increasing problem during the last two decades. The hospital-wide incidence of candidaemia in the UK is approximately 3 per 100 000 bed days, and 40% to 52% of all cases occur in the intensive care unit (ICU).1–3

National surveillance studies have shown that the incidence of infection varies greatly between different types of ICUs.4 Among surgical ICUs (SICUs), the candidaemia rate can vary as much as 0.50–1.73 per 1000 patient days.5 In general, ICUs caring for high-risk patients such as abdominal surgical or immunosuppressed patients have a higher incidence of invasive candidiasis than general medical ICUs/SICUs as illustrated by the National Epidemiology of Mycosis Survey study.6 The difference in infection rates is mainly due to the patient case mix and risk factors, but may also be influenced by the specific management of the infection in particular units. There are a number of well-described general risk factors such as old age, very low birth weight in premature neonates, diabetes mellitus and immunosuppression.7,8 In addition, multivariate analyses have identified some specific independent risk factors in SICU patients (Table 1).7,8

Candidaemia is associated with considerable morbidity in critically ill patients leading to an overall prolonged ICU stay, a longer duration of mechanical ventilation and haemodialysis.9,10 The attributable mortality is 38%,11 although it can vary between 5% and 71%.12–14 The economic burden of a candidaemia case in an ICU has been estimated to be in the region of €16 000.15 Because of the substantial morbidity, mortality and economic cost of invasive candidiasis, the appropriate management of this infection is important.

Candida colonization and the role of screening

Candida species frequently colonize non-sterile sites in the body, particularly the skin, mouth, gut and genitals. In SICU patients, the most frequently colonized sites are the oropharynx (63%), urine (25%) and gut (11%), but Candida can also be found in other areas such as the lumen of medical devices including urinary catheters and wound drains.16 The risk of colonization increases with the duration of the ICU stay, the use of urinary catheter and the use of antibiotics such as vancomycin or imipenem.17,18

Typing of Candida isolates has shown that those patients who develop invasive candidiasis have previously been colonized by the same strain with a median time from colonization to infection of 8 days.19,20 Unfortunately, there are no validated laboratory markers that can reliably predict or detect early invasive candidiasis in ICU patients. In the past, researchers have tried to predict infection by measuring the Candida colonization of distinct body sites (upper respiratory or stomach samples, urine and wound swabs) divided by the number of sites tested, which became known as the colonization index (CI).20 Although the negative predictive value was 100%, the positive predictive value for candidaemia was relatively low (66%) and could only be improved if the CI was corrected by quantitative culture. The cost effectiveness of screening all patients is relatively low, as not every patient is at a high risk of Candida infection. Nevertheless, it is advisable to record and speculate all Candida from clinical samples of ICU patients in order to aid empirical antifungal treatment if it becomes clinically necessary.

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For patients who do not have multi-organ failure or severe sepsis, fluconazole may be used for the empirical treatment of candidaemia. A broad-spectrum antifungal agent such as amphotericin B or an echinocandin (discussed later) may be used if the patient is haemodynamically unstable or if the patient is known to be colonized with a fluconazole-resistant strain such as *Candida krusei*.

The treatment of proven invasive candidiasis/candidaemia is mainly guided by the *Candida* species and host factors (Figure 1). The treatment response of older and newer antifungal agents varies between 60% and 90% (Table 2). The relatively new group of echinocandins (caspofungin, micafungin and anidulafungin) has shown a particularly good efficacy of 73% to 90% in the treatment of candidaemia, although some studies have not been fully published. In addition, the broad-spectrum anti-candidal activity, good safety profile (low renal and liver toxicity) and low interaction with other drugs make this group of drugs an attractive choice for the empirical or first-line treatment of candidaemia in critically ill patients, in particular those with multi-organ failure or immunosuppression. Some caution should be taken in treating *Candida parapsilosis*.

### Table 1. Independent risk factors for the development of candidaemia in SICU patients

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>RR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior abdominal surgery</td>
<td>7.3</td>
<td>—</td>
</tr>
<tr>
<td>Triple lumen catheter</td>
<td>5.4</td>
<td>—</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>4.2</td>
<td>—</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>3.6</td>
<td>—</td>
</tr>
<tr>
<td>Multiple antibiotics (3–5)</td>
<td>—</td>
<td>12.5</td>
</tr>
<tr>
<td><em>Candida</em> isolated from other sites</td>
<td>—</td>
<td>10.4</td>
</tr>
<tr>
<td>Length of ICU stay &gt;7 days</td>
<td>—</td>
<td>9.8</td>
</tr>
</tbody>
</table>

RR, relative risk; OR, odds ratio.
Modified from Blumberg et al. and Wey et al.

### Management of candidaemia in the ICU

Once *Candida* has been isolated from the bloodstream or other types of invasive candidiasis have been diagnosed, it should be acted on promptly. The infection should be treated early (within 48 h) with an appropriate antifungal agent to reduce mortality unless all active treatment has been withdrawn. Without treatment, candidaemia has been associated with a high mortality (58%). The majority of ICU patients (87% to 98%) acquiring candidaemia have intravascular lines in situ, which should be removed whenever possible as the failure to do so can prolong the candidaemia and also increase the mortality.

Treatment is also advisable in asymptomatic patients with positive *Candida* blood cultures obtained from vascular lines, as one cannot predict which patient may develop infectious complications such as endocarditis or endophthalmitis. Fungal endogenous endophthalmitis is one of the most common complications following candidaemia with an incidence of 9% to 15% in ICU patients. Fundoscopy is therefore recommended in all candidaemia patients and treatment may have to be adjusted accordingly.

For the treatment of invasive candidiasis, there are a range of old and new antifungal agents available that vary in their spectrum of activity, pharmacokinetics, drug–drug interactions, side effects and efficacy. The choice of antifungal agent depends mainly on two factors: firstly, the available information on the causative *Candida* (species and susceptibility) and secondly, on patient-specific factors that include the site of infection, haemodynamic stability, organ failure and concomitant use of other drugs such as immunosuppressants. If the causative *Candida* species is not yet known or evidence of infection is based only on histology/microscopy, the first-line antifungal treatment is empirical and has to be based on the local resistance profile of *Candida* species in the ICU. Azole-resistant or non-*albicans* strains may be more prevalent in patients who have previously been exposed to azoles. Overall, fluconazole-susceptible *Candida albicans* remains the most common species causing candidaemia in ICU patients. However, other *Candida* species are emerging as significant pathogens as shown by the national surveillance studies in the USA that reported an increase in the adult candidaemia due to *Candida glabrata*. This species has a reduced susceptibility to fluconazole and is the second most common species causing candidaemia in adults in many countries.

### Table 2. Clinical efficacy of antifungal agents for the treatment of invasive candidiasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study type</th>
<th>Response (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>RB</td>
<td>73.4</td>
<td>Mora-Duarte et al.</td>
</tr>
<tr>
<td>dAmB</td>
<td></td>
<td>61.7</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>RDB</td>
<td>89.6</td>
<td>Ruhnke et al.</td>
</tr>
<tr>
<td>LipAmB</td>
<td></td>
<td>89.5</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>RDB</td>
<td>75.6</td>
<td>Reboli et al.</td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
<td>60.2</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>R</td>
<td>65.0</td>
<td>Kullberg et al.</td>
</tr>
<tr>
<td>dAmB/fluconazole</td>
<td></td>
<td>71.0</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>R</td>
<td>70.0</td>
<td>Rex et al.</td>
</tr>
<tr>
<td>dAmB</td>
<td></td>
<td>79.0</td>
<td></td>
</tr>
</tbody>
</table>

dAmB, amphotericin B deoxycholate; LipAmB, liposomal amphotericin B; RB, randomized blind control; RDB, randomized double-blind control; R, randomized.

*a*Non-inferiority study.
infections, as in vitro susceptibility testing of echinocandins has shown high MICs. This group of antifungal agents also penetrates the blood–brain and blood–ocular barrier poorly, and more conventional agents such as amphotericin B, 5-flucytosine or azoles may need to be used for the treatment of CNS infections or fungal endophthalmitis. Once a patient has been started on antifungal treatment with any agent, it is advisable to repeat blood cultures after 5–7 days to monitor breakthrough infections and response. Most uncomplicated candidaemia cases are treated for ≥14 days from the last negative blood culture and resolution of symptoms.

Preventative measures and the role of antifungal prophylaxis

Part of the management of candidiasis is the prevention of invasive infection. Interventions to minimize risk factors such as good operative technique, control of diabetes mellitus, prudent antibiotic use and good line care policies may help prevent Candida infections. An Australian study estimated that 86% of the central venous catheter-related candidaemias could be prevented if the lines were changed after 1 week of insertion. Many ICUs already implement such measures, and the question is whether the use of antifungal prophylaxis can reduce the incidence of invasive candidiasis further.

Fluconazole prophylaxis has been shown to significantly reduce the risk of invasive candidiasis in neutropenic patients, and its use is well established in many haematology units. However, the effectiveness and role of antifungal prophylaxis for non-neutropenic ICU patients are less clear. There have been a number of studies addressing the efficacy of fluconazole prophylaxis in SICU patients. A recent meta-analysis of four randomized placebo-controlled trials was able to demonstrate that fluconazole reduced the overall Candida colonization rate of patients. However, no reduction in the infection rate or survival advantage could be demonstrated, although the incidence of candidaemia may have been too low in these studies to make firm assumptions. It remains unclear whether the use of prophylaxis can reduce the morbidity such as the length of ventilator or ICU bed days. Little is known about the longer-term risks of broadly applied antifungal prophylaxis in terms of resistance development or shift to non-C. albicans strains.

Conclusions

Invasive candidiasis is a serious condition in ICU patients that requires early and appropriate management in order to reduce morbidity and mortality. A number of older and newer antifungal agents are available, and the choice should be guided by the Candida species and patient-specific factors. The wide use of antifungal prophylaxis or screening is generally not recommended, although it may be of benefit for a highly selective small group of high-risk patients.

Transparency declarations

None to declare.

References