Management of fungal infections in the intensive care unit: a survey of UK practice†

C. M. Chalmers1,3* and A. M. Bal2
1 Department of Anaesthesia and 2 Department of Microbiology, Crosshouse Hospital, Kilmarnock KA2 0BE, UK
3 Present address: Department of Anaesthesia, Gartnavel General Hospital, Glasgow G12 9YN, UK
* Corresponding author. E-mail: kitchalmers@doctors.org.uk

Editor’s key points
- Candida bloodstream infections are common in intensive care unit (ICU) patients.
- This survey of UK ICUs found that the majority had no documented treatment protocol.
- Most units administer empirical antifungal drugs to at-risk patients.
- The response rate was low (30%) and further data are needed.

Background. Candida species are a common cause of nosocomial bloodstream infection. Such infections commonly affect patients in the intensive care unit (ICU) and carry a high mortality. There are published guidelines for the management of fungal infections, but there are no data on the usual management of invasive Candida infections in UK ICUs.

Methods. An electronic survey was sent by email to a representative clinician in 236 ICUs, over 90% of units in the UK. Questions related to the institution of empirical therapy and to the management of proven candidaemia.

Results. There were 72 responses. A minority of units follow a policy regarding the management of these infections but the involvement of microbiologists is usual. Empirical therapy is used in 85.9% of units, often for patients perceived to be at high risk. Fluconazole is the most commonly used antifungal agent, both for empirical therapy and for the treatment of proven candidaemia. For candidaemic patients, 73.9% of ICUs frequently or always remove central venous catheters within 48 h, while 15.1% frequently or always arrange ophthalmology review.

Conclusions. Management of fungal infections is relatively consistent among responding units. However, recent developments in the field have not yet been incorporated into standard practice. Adherence to published guidelines could be improved, potentially reducing morbidity and mortality from these common infections.

Keywords: candidiasis; candidiasis invasive; data collection; health-care surveys; intensive care

Accepted for publication: 7 February 2011

Candida species are a common cause of nosocomial bloodstream infection, accounting for ~3% and 10% of all cases of nosocomial infections in Europe1,2 and the USA,3 respectively. The mortality associated with candidaemia in the UK continues to be high: our own unpublished data, collected from five centres in the UK during 2008, show a mortality of 40%, similar to that found in earlier studies.4 This is despite the advent of new antifungal agents and the publication of management standards and guidelines. These documents, published by the British Society for Medical Mycology (BSMM)5 and the Infectious Diseases Society of America (IDSA),6 between them recommend choice, dose, and duration of antifungal therapy for candidaemia, and other management strategies such as removal of central venous catheters (CVC) and ophthalmological review for all candidaemic patients.

Epidemiological studies have consistently identified intensive care unit (ICU) patients as a high-risk group for Candida bloodstream infections, with 28–47% of episodes occurring in these patients.3,4,7,8 In the UK, the incidence of candidaemia in ICUs is 1.26 cases per 1000 occupied bed-days7 or 0.74 per 100 admissions.8 Despite the importance and frequency of these infections, there are no UK-based studies documenting their usual management.

Therefore, we conducted a national survey on the ICU management of Candida infections in the UK. The aims were to obtain information on local expertise and policies, selection of antifungal agents, and attitudes to and practice regarding empirical therapy and the management of patients with proven candidaemia, including adherence to published guidelines. A summary of the main results has been published in abstract form.9

Methods
The West of Scotland Research Ethics Service confirmed, on the basis of the nature of the study, that formal ethical
A review was not required. An electronic questionnaire was designed using SurveyMonkey™ (www.surveymonkey.com) (Fig. 1). This was sent by email to one clinician in most ICUs in England, Northern Ireland, Scotland, and Wales. In Scotland, contact details were obtained from the Scottish Intensive Care Society Audit Group (SICSAG) and the survey was sent to a representative of all 24 units in the country. It was not possible to obtain contact details for ICUs in the other countries, but the Intensive Care National Audit and Research Centre (ICNARC) agreed to distribute the survey. The ICNARC network includes ≏90% of all ICUs in England, Northern Ireland, and Wales, some of which are combined ICU and high-dependency unit. Using this network, the survey was distributed to a representative in 212 units in these countries. A single email reminder was sent to all 236 recipients ~3 weeks after the first communication. This yielded only six additional responses and no further reminders were sent.

Questions related to the management of non-neutropenic patients admitted to the ICU; this was stated on the first page of the survey. Respondents were encouraged to provide an answer based on usual practice in their unit,

### General questions

1. Do you have a policy on the use of antifungal agents? *(multiple answers possible)*
   - No / Yes – a policy for the hospital / Yes – a policy specifically for ICU
2. Do you take microbiology advice before commencing antifungal agents?
   - Never / Infrequently / Frequently / Always
3. Which sites do you normally screen for *Candida* infection/colonisation? *(multiple answers possible)*
   - None: do not screen / Sputum or tracheal aspirate / Mouth / Urine / Central line site / Arterial line site / Wounds / Fluid / Other *(please specify)*
4. Does anyone in your unit have a specific interest in fungal infections in the ICU?
   - Yes / No

### Regarding empirical treatment

1. Do you ever use antifungal agents empirically?
   - Yes / No

**Questions 2–5 were shown only to those answering ‘Yes’ to question 1 above.**

2. Which patients might you treat empirically?
   - Any patient / Specific subgroup(s) of patients *(please specify, e.g. medical/surgical)*
3. Which of the following is likely to prompt empirical treatment in your unit:
   - List presented twice: 1) As a single factor 2) in combination with other factors *(multiple answers possible in each case)*
   - Fever with no response to antibiotics / Rising inflammatory markers / Prolonged ICU stay / Isolation of *Candida* from a single site / Isolation of *Candida* from multiple sites / Other *(state)*
4. For empirical treatment, which is your usual antifungal agent of choice?
   - Amphotericin – conventional / Amphotericin – liposomal / Caspofungin / Fluconazole / Voriconazole / Other *(please specify)*
5. Have you seen a benefit from the empirical use of antifungal agents?
   - No / Yes – benefit generally perceived, no formal study carried out / Yes – confirmed by study

### Regarding confirmed candidaemia

1. When *Candida* is found in blood cultures, prior to species identification which is your usual antifungal agent of choice?
   - Amphotericin – conventional / Amphotericin – liposomal / Caspofungin / Fluconazole / Voriconazole / Other *(please specify)*
2. Do you switch therapy (e.g. from voriconazole/caspofungin to fluconazole) if the candida isolate is confirmed as *C. albicans*?
   - Yes / No – usually start with Fluconazole / No – see no need for change
3. Do you use combination antifungal agents?
   - Never / Infrequently / Frequently / Always
4. Do you remove central lines within 48 hours for patients with candidaemia?
   - Never / Infrequently / Frequently / Always
5. Do you arrange ophthalmology review for patients with candidaemia?
   - Never / Infrequently / Frequently / Always
6. How long do you continue antifungal therapy for candidaemia?
   - 7 days / 14 days / 21 days / Dependent on clinical response / Other *(please specify)*

---

**Fig 1** Questions and possible answers presented in the electronic survey. Except where indicated, only a single answer was possible.
rather than their own personal preferences. Responses were imported into a Microsoft Excel spreadsheet for further analysis.

**Results**

Seventy-two responses were received from the 236 surveys sent, giving an overall response rate of 30.5%. The response rate was 54.2% (13/24) in Scotland and 27.8% (59/212) in the rest of the UK. Six of the 72 responses (8.3%) were incomplete; hence, the denominator varies in the observations below.

**General information**

There is a clinician with a special interest in fungal infections in 20% of units (14/70). The majority of units (57.7%, 41/71) have no documented policy on the use of antifungal agents. The remaining units follow a policy which is either specific to the ICU (15.5%, 11/71) or in general use throughout the hospital (28.2%, 20/71). Microbiological advice is frequently or always sought before commencement of antifungal therapy in 54.2% (39/72) and 40.3% (29/72) of units, respectively. The sites most frequently screened for colonization or infection with *Candida* are respiratory secretions, wounds, and urine (Table 1). Four of the six free-text answers stated that all microbiological specimens are screened for *Candida* by the local laboratory.

**Regarding empirical treatment of infections**

Antifungal agents are used empirically in 85.9% of units (61/71). The remaining questions on empirical treatment were shown only to these 61 respondents. Fluconazole was the most commonly used empirical antifungal agent (Table 2). The three free-text answers regarding the choice of the antifungal agent stated the use of anidulafungin, combination of liposomal amphotericin B and posaconazole, and any of fluconazole, caspofungin, or micafungin. Empirical treatment would be considered for any patient in 35.1% of units (20/57), whereas 64.9% (37/57) would consider this only for patients in certain high-risk groups. The definition of a high-risk group varied amongst these 37 respondents (Table 3). The groups most commonly suggested include patients with gastrointestinal conditions, immunocompromise, liver failure, or a combination of factors (examples cited included fever, total parenteral nutrition, broad-spectrum antibiotics, and prolonged ICU stay). The majority of respondents (76.4%, 42/55) believe empirical therapy to be beneficial.

Table 2 Usual choice of antifungal agent for empirical therapy and for the treatment of proven candidaemia. The number of responses (%) for each answer option is shown. See text for answers given as ‘other’

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Empirical therapy</th>
<th>Proven candidaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin: conventional</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amphotericin: liposomal</td>
<td>2 (3.4)</td>
<td>6 (9.4)</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>4 (6.8)</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>48 (81.4)</td>
<td>41 (64.1)</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>2 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4.2)</td>
<td>6 (9.4)</td>
</tr>
<tr>
<td>Total no. of responses</td>
<td>59</td>
<td>64</td>
</tr>
</tbody>
</table>

Table 3 Patient groups in which empirical antifungal therapy might be considered. Comments were given by the 37 respondents who said that they would empirically treat only certain groups of patients. Many of these respondents named more than one patient group. Responses stating ‘neutropenic patients’ or ‘neutropenic sepsis’ were discounted, since the survey related only to non-neutropenic patients

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. (%) of responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Other abdominal surgery or perforation, intra-abdominal sepsis</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Upper GI surgery or perforation</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Combination of factors leading to perceived high risk</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Haematology or other oncology patients</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Surgical patients</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Prolonged or multiple antibiotics</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Patients with suggestive clinical history or symptoms</td>
<td>2 (5)</td>
</tr>
<tr>
<td>GI perforation only if prolonged or untreated</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Medical patients</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Long-stay surgical patients</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Military casualties</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Transplant patients</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Long term steroids</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>
therapy if present in combination. Isolation of *Candida* from multiple non-invasive sites is the only factor likely to prompt empirical therapy if present alone. The six free-text responses included combinations or variations of the given triggers, microbiological advice, and other factors leading to perceived high risk, such as gastrointestinal surgery or perforations.

**Regarding treatment of proven candidaemia**

Fluconazole is the most commonly used agent for therapy of proven candidaemia (Table 2). One free-text answer stated that anidulafungin is used and others that the agent used is dependent on microbiological advice, patient group, or consultant preference. Of those who respond that fluconazole is not a first-choice agent, 77% (21/27) would change therapy to fluconazole if the species were subsequently identified as *Candida albicans*. Only one unit frequently uses combination antifungal agents for therapy. The duration of antifungal therapy is 7 days in 3% of units (2/66), 14 days in 47% (31/66), 21 days in 6.1% (4/66), and at least 3 weeks in 1.5% (1/66). Some units do not give therapy for a specified number of days, but base the duration on clinical response (22.7%, 15/66) or microbiological advice (10.6%, 7/66). Other free-text responses usually stated that the duration of therapy is variable depending on some combination of patient and clinical factors.

CVC are removed within 48 h of documentation of candidaemia always in 35.4% (23/65), frequently in 38.5% (25/65), infrequently in 21.5% (14/65), and never in 4.6% (3/65) of units. Ophthalmology review is arranged always in 4.5% of units (3/66), frequently in 10.6% (7/66), infrequently in 34.8% (23/66), and never in 50% (33/66).

**Discussion**

Our results show that the management of fungal infections is relatively consistent among responding units. Close liaison with microbiologists is common, but some of our data suggest that recent developments in the field have yet to impact on current management.

> Over 80% of responding units use empirical antifungal therapy and this is generally perceived to be beneficial. Its use is often reserved for groups of patients considered to be high risk, or individuals with a combination of clinical risk factors. The IDSA recommends considering empirical antifungal therapy for critically ill patients with clinical risk factors for invasive candidiasis and no other known cause of fever, but note that there is little evidence to support this approach. The sole randomized controlled trial of empirical antifungal therapy in ICU patients found no benefit of using fluconazole vs placebo, with successful composite outcome demonstrated in 36% and 38% of each group, respectively. Recognized risk factors in the existing literature are broadly consistent with those cited by survey respondents and include immunosuppression, broad-spectrum antibiotics, acute renal failure, and disorders compromising integrity of the gastrointestinal tract. Scoring systems have been developed to identify individual patients who may benefit from empirical therapy, but these are not yet fully validated. Although definitive diagnosis of invasive candidaemia is notoriously difficult, there is a risk that the widespread use of antifungal agents empirically may select for resistant organisms. We believe that in the light of the current data, the use of empirical therapy may often not be justified and should be used with caution.

For both proven candidaemia and empirical therapy, the IDSA recommends using echinocandins (e.g. caspofungin) first-line for those who are moderately or severely ill, with intention to switch to fluconazole if appropriate after species identification. Among survey respondents, fluconazole is the most commonly used antifungal agent. Although fluconazole is cheap, well-tolerated, and effective against many *Candida* species, some non-*albicans* species may be inadequately treated. *Candida glabrata* causes 15–18% of *Candida* infections in ICU patients and often displays some resistance to fluconazole, but is sensitive to echinocandins. Echinocandins, unlike fluconazole, are fungicidal and are active against biofilms. The apparent reluctance to use echinocandins first-line is in keeping with ICU practice elsewhere in Europe and may reflect concern regarding cost. However, inadequate treatment of candidiasis correlates with greater cost per patient and higher mortality. If fluconazole is chosen, the high doses recommended by the IDSA (800 mg loading dose, 400 mg daily) should ideally be used.

Both the IDSA and the BSMM recommend removal of CVC within 48 h of identification of candidaemia. Published audits, including but not confined to intensive care, have found that this target is achieved in 79–84% of patients. Our lower figure of 74% might reflect awareness of this recommendation, but it is recognized that in unstable patients, the risks of CVC removal may outweigh the potential benefits. Moreover, the evidence that their retention increases mortality remains controversial, since patients with CVC are likely to be more unwell and predisposed to higher mortality. A recent literature review found only one study, demonstrating definite benefit from early CVC removal.

<table>
<thead>
<tr>
<th>Factor</th>
<th>As a single factor</th>
<th>If combined with other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever with no response to antibiotics</td>
<td>6 (10.3)</td>
<td>46 (79.3)</td>
</tr>
<tr>
<td>Rising inflammatory markers</td>
<td>1 (1.7)</td>
<td>42 (72.4)</td>
</tr>
<tr>
<td>Prolonged ICU stay</td>
<td>3 (5.2)</td>
<td>33 (56.9)</td>
</tr>
<tr>
<td>Isolation of <em>Candida</em> from single site</td>
<td>1 (1.7)</td>
<td>28 (48.3)</td>
</tr>
<tr>
<td>Isolation of <em>Candida</em> from multiple sites</td>
<td>24 (41.4)</td>
<td>30 (55.2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (5.2)</td>
<td>6 (10.3)</td>
</tr>
<tr>
<td>Total no. of responses</td>
<td>58</td>
<td>58</td>
</tr>
</tbody>
</table>
Ocular candidiasis occurs in 9% of patients with candidaemia. The IDSA recommends that all patients with candidaemia undergo ophthalmological examination and states that this is particularly important in patients who cannot communicate visual disturbance, making this highly relevant to ICU patients. A finding of Candida endophthalmitis may influence the choice or duration of antifungal therapy or indicate the need for surgical intervention. Our data suggest that an ophthalmological review is rarely sought in UK ICUs, perhaps because of low awareness of this complication or the guidelines, or organization of services.

This survey is limited by the usual problems of self-selection of respondents and the constraints of question wording. The response rate of 30%, in particular, limits the conclusions which can be drawn. It was not possible to use alternate means of obtaining responses, for example, by telephone, since we had no access to contact details for the vast majority of recipients. However, the results represent the best information available on current ICU practice. Important findings are the common use of empirical therapy targeted to certain patients, the continuing popularity of fluconazole as a first-line agent, and relatively low rates of CVC removal and ophthalmology review in candidaemic patients. We conclude that given the mortality and morbidity associated with these infections and their frequency in ICU patients, there is a need for greater awareness among UK intensivists of the current standards and guidelines relating to their management.

Conflict of interest
A.M.B. has accepted conference invitations from manufacturers of echinocandins including Astellas, MSD, and Pfizer, received honoraria from Pfizer for attending advisory board meetings, signed a contract for attending advisory board meetings with MSD, and has lectured on behalf of Astellas for a fee. A.M.B. has also undertaken research partially sponsored by Astellas.

References
11 Kauffman CA. Epidemiology and pathogenesis of candidemia in adults. In: Basow DS, ed. UpToDate, Waltham, MA: UpToDate, 2010