

## Original papers

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### Candidaemia in a large teaching hospital: a clinical audit

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#### Summary

**Background:** Candidaemias are associated with significant morbidity and mortality. The British Society of Medical Mycology and Infectious Diseases Society of America recently published audit standards, to address the changing epidemiology of candidaemia and to improve outcomes.

**Aim:** To investigate the local epidemiology of candidaemia and the standard of care in a large teaching hospital.

**Design:** Retrospective audit.

**Methods:** Data were obtained for all candidaemia episodes over the 4-year period ending July 2004, from the medical and nursing notes, laboratory computer and patient administration system.

**Results:** We identified 92 episodes in 90 patients. The main predisposing factors were being on an intensive care unit, having a central venous catheter, and (for neonates) prematurity. Central venous catheters were removed at a mean 1.8 days following candidaemia; 79% (37/47) were removed within 48 h (the audit standard). Identification and susceptibility tests were

performed for 94.7% of isolates. All were susceptible to amphotericin B; 87% were susceptible to fluconazole. Antifungal treatment was started within 24 h of a positive blood culture in 84% of episodes. Initial antifungal therapy was appropriate in 95% (61/64) of treated cases. Most patients (81%) who survived or completed their intended course of treatment before death received at least 2 weeks treatment. However, only 45% of those transferred to other hospitals had accompanying guidance on the intended further duration of therapy. Thirty-day mortality was 41%. After adjustment for age, the presence of *Candida*-related complications was associated with an odds ratio for mortality of 6.5 (95% CI 1.2–36.5,  $p=0.03$ ).

**Discussion:** Overall the audit standards set by the BSMM and IDSA were met, and discrepancies did not lead to a change in outcome. Improved intravenous catheter care, a more pro-active approach to searching for complications, and improvement in the inter-hospital transfer process, will assist in reducing morbidity and mortality.

#### Introduction

Between 1997 and 2002, candidaemias were the eighth most common cause of hospital-acquired

bloodstream infection in the UK.<sup>1</sup> Many studies have shown a rising incidence, with mortality >25% in

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recent UK series.<sup>2,3</sup> The diagnosis and subsequent treatment of candidaemia is associated with increased mortality, length of hospital stay and costs.<sup>4</sup> Its epidemiology appears to be evolving, with a rise in non-albicans species with reduced susceptibilities to fluconazole (e.g. *Candida krusei* and *Candida glabrata*).<sup>2,5-7</sup>

In response to this changing epidemiology, and in an attempt to reduce mortality, audit standards were introduced for clinical services, clinical microbiology laboratories, radiology departments and histopathology departments by the British Society for Medical Mycology (BSMM).<sup>8</sup> Treatment type and duration was also audited against the most recent Infectious Diseases Society of America (IDSA) guidelines.<sup>9</sup> Mortality was shown to improve in a prospective audit assessing patient outcome with the use of the IDSA guidelines.<sup>10</sup> We performed a retrospective audit of candidaemias to determine how well these criteria were being met by our microbiology and clinical departments, and to provide local epidemiological data that can be used to improve clinical practice.

The objectives of the audit were: (i) to describe the occurrence of candidaemia and the characteristics of patients in whom it was diagnosed; (ii) to determine the current clinical standard of care for patients with candidaemia and its impact on patient morbidity and mortality; and (iii) to propose strategies to improve patient outcome and standard of care in line with current BSMM guidelines. Audit standards were as published by the BSMM<sup>8</sup> and IDSA.<sup>9</sup>

## Methods

Addenbrooke's Hospital, Cambridge is a teaching hospital with approximately 1100 beds, with almost 62 000 in-patient episodes per year. It offers a number of specialist services providing organ transplantation (liver, kidney, small bowel and pancreas), haematology/oncology (including stem cell transplantation), infectious diseases, neurosurgery and intensive care (including neonatal, paediatric and neurocritical care and general adult) facilities.

We performed a retrospective audit of candidaemias for the 4-year period ending July 2004. Approval for the study was obtained from the hospital's audit committee. A positive blood culture was regarded as part of a single episode if it occurred within 14 days of a previous positive blood culture. Subsequent positive blood cultures that occurred after this time were considered to be recurrences. Data were obtained from the medical and nursing notes, laboratory computer and Patient Administration System, and entered onto a standard database. Data obtained

included age, gender, ward, diagnosis, predisposing factors, presence/duration of central venous catheters, germ-tube result, *Candida* speciation and susceptibility, timing, dosage and duration of antifungal treatment, presence of complications and outcome at 30 days. Severity of underlying disease was assessed using the McCabe classification.<sup>11</sup> Time to treatment was altered from 6 to 24 h for the purpose of analysis. Statistical significance was assessed using Pearson's  $\chi^2$  test (or the exact test where appropriate) for proportions and by t-test or appropriate non-parametric alternatives when distributional assumptions were in doubt.  $p < 0.05$  was taken to indicate statistical significance. The relative odds of death for various clinical and demographic parameters were calculated by logistic regression analysis. The effect of age and McCabe score were adjusted for in a multivariable model. Analyses used the statistical software Stata (version 8).

Blood cultures were processed using the BacT/Alert 3D system (bioMerieux). Isolates were grown on Columbia blood agar and Sabouraud's dextrose agar (Oxoid). Germ-tube testing was performed on all *Candida* isolates as a rapid identification tool for *C. albicans*. This involved inoculating colonies to rabbit plasma, incubating at 37°C for 2 h and observing for the presence of germ tubes. Further identification and susceptibility tests were done at the regional Health Protection Agency (HPA) Mycology Reference Laboratory, using a variety of tests including Auxacolor 2 (Bio-Rad), API 20C AUX (bioMerieux) and nucleic acid amplification tests. Susceptibility testing used microtitre minimum inhibitory concentrations.

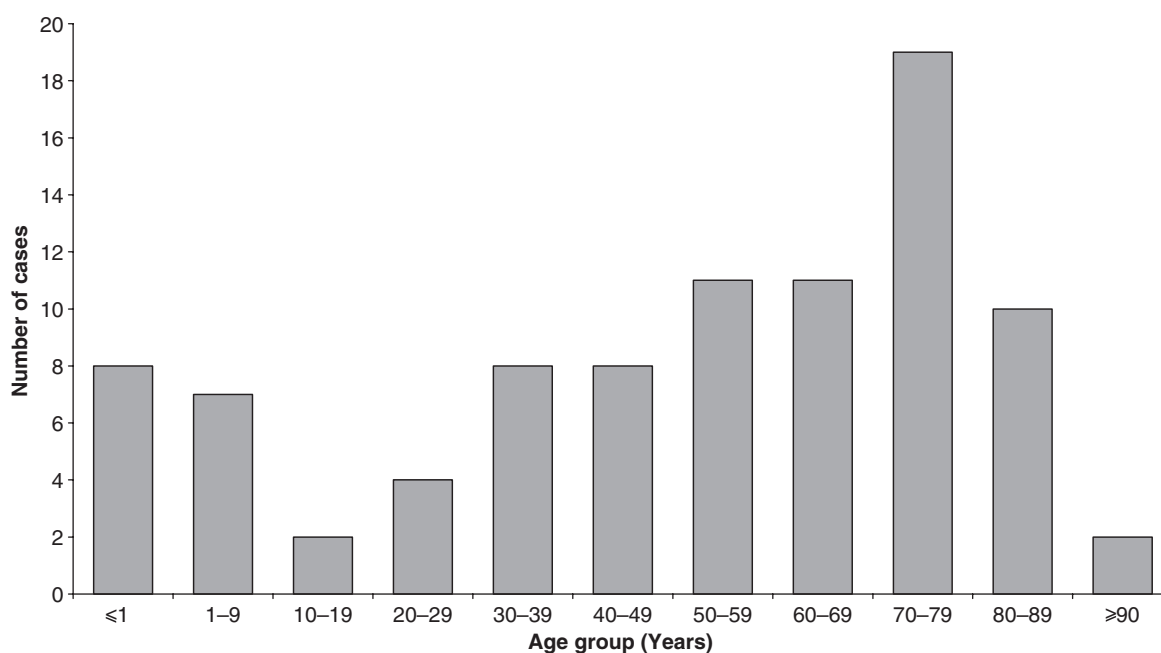
## Results

There were 92 episodes in 90 patients during the study period. Sixteen episodes occurred in year 1, 21 in year 2 (two mixed infections), 25 in year 3 and 30 in year 4 (one mixed infection; 2 recurrences). There was no consistent increase in the number of non-albicans *Candida* isolates over the study period (Table 1). However, marked variability in the proportion of *C. albicans* isolates was noted: 25.0% (4/16), 37.5% (9/24), 68.0% (17/25) and 46.7% (14/30) in years 1, 2, 3 and 4, respectively. The majority of patients were male (63.7%) with a median age of 56 years (IQR 34–74 years) (Figure 1). Forty-two patients were from the adult intensive and neurocritical care units. Of the critical care patients, 17 were from general surgery, 16 were general medical patients, five were neurosurgical patients, three were hepatology cases (two liver transplant recipients) and one was a

**Table 1** Breakdown of *Candida* isolates according to species and year of isolation

	Year 1 Aug 00–July 01	Year 2 Aug 01–July 02	Year 3 Aug 02–July 03	Year 4 Aug 03–July 04
No. of episodes/year <sup>a</sup>	16	21	25	30
<i>C. albicans</i>	4 (25.0%)	9 (37.5%)	17 (68.0%)	14 (46.7%)
Non-albicans <i>Candida</i>	11 (68.8%)	14 (58.3%)	8 (32.0%)	13 (43.3%)
<i>Candida</i> sp. (not identified)	1 (6.3%)	1 (4.2%)	0 (0.0%)	3 (10.0%)
<i>C. glabrata</i>	5 (31.3%)	10 (41.7%)	1 (4.0%)	7 (23.3%)
<i>C. parapsilosis</i>	3 (18.8%)	2 (8.3%)	3 (12.0%)	2 (6.7%)
<i>C. tropicalis</i>	1 (6.3%)	0 (0.0%)	2 (8.0%)	2 (6.7%)
<i>C. krusei</i>	1 (6.3%)	2 (8.3%)	1 (4.0%)	0 (0.0%)
<i>C. lusitanae</i>	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
<i>C. guilliermondi</i>	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (3.3%)
Total (isolates)	16	24	25	30

<sup>a</sup>Percentages not presented because some episodes had more than one isolate.

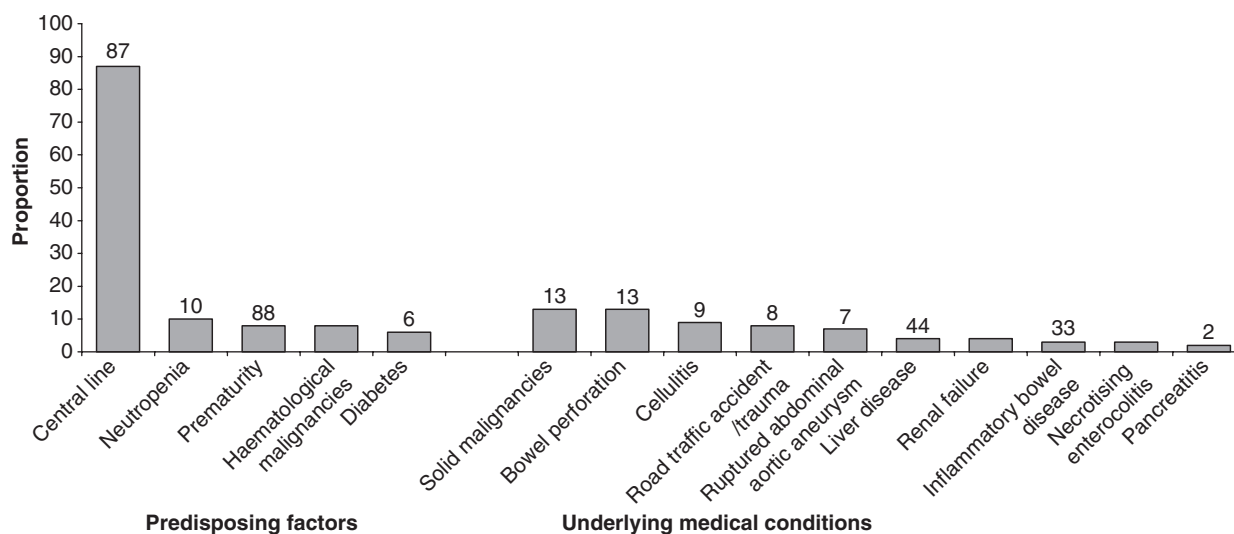
**Figure 1.** Age distribution of patients.

renal transplant recipient. Nine cases occurred in the neonatal and paediatric intensive care units. There were seven adult oncology patients, five of which were haematological malignancies, and five paediatric oncology patients. There were 14 general medical patients, eight general surgery, two orthopaedic surgery, two general paediatric patients and one hepatology patient.

### Predisposing factors for candidaemia

The most common predisposing factor for candidaemia was a central venous catheter, which

was present in 78 episodes (84.7%). Presence on a critical care unit was also a predisposing factor, for both the paediatric and adult groups (56%). Prematurity was a predisposing factor among the neonatal group. All eight neonatal cases had a gestational age below 34 weeks; 75% (6/8) were <25 weeks old, of whom 83% (5/6) weighed <1 kg at birth. Central venous lines were present in all the neonates (with parenteral feeding in 75%) and necrotizing enterocolitis (NEC) was observed in more than a third (3/8) of cases. No episodes of candidaemia occurred in intravenous drug users or HIV-seropositive individuals. Co-morbidities



**Figure 2.** Distribution of candidaemia cases based on predisposing factors/underlying medical condition. Total proportions exceed 100%, because patients may have more than one predisposing factor.

and predisposing factors are shown in Figure 2. Nineteen patients had one co-morbidity while twenty patients had three or more co-morbidities. The majority of patients (54) had a McCabe score of class 1 (non-fatal underlying disease) while a smaller proportion (28) had a score of 2 (ultimately fatal disease) and only eight patients had a score of 3 (rapidly fatal underlying disease).

The central venous line had been in place for a mean duration of 28.8 days (SD 117 days) before candidaemia occurred. No information was obtained for two episodes. Patients with a central venous catheter stayed in hospital on average twice as long (18 days) as those without a catheter (9 days). Central venous catheters were taken out on average within 1.8 days after the blood culture result. Thirty-seven central venous catheters (79%) were removed within the audit standard of 48 h. Less than half (27/61) of catheter line tips were positive for candida on culture.

### Germ tube test as a rapid tool for identification

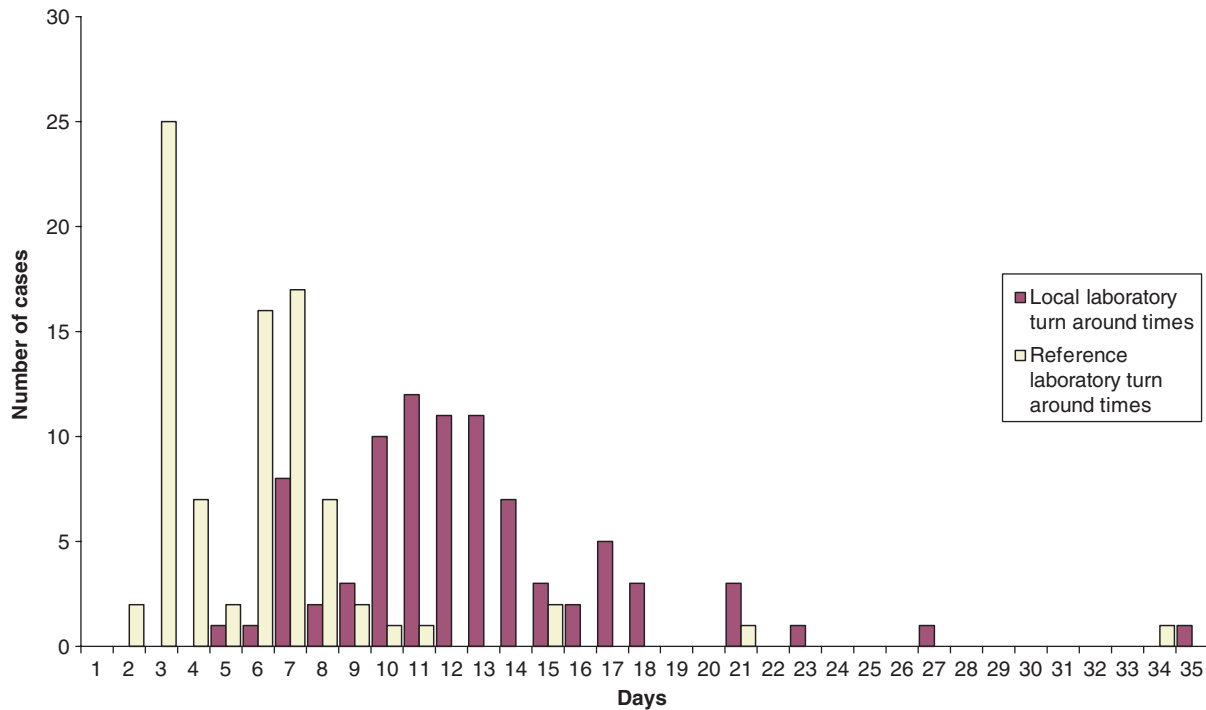
The germ tube test was highly sensitive (97.5%) when used for the rapid identification of *C. albicans*. However, four non-*albicans Candida* strains were initially reported as germ tube-positive but identified as *C. tropicalis* by the reference laboratory. The specificity of the germ tube test for identifying *C. albicans* was 90.5%, with a positive predictive value of 90.9% and a negative predictive value of 97.4%. Isolates not formally identified by the

reference laboratory and mixed candidaemia episodes were excluded, as the germ tube result is unreliable in this instance.

### Identification and susceptibility testing

Ninety isolates (94.7%) were sent for identification and susceptibility testing. Identification and susceptibility test results took an average of 12 days (IQR 10–14 days) to obtain from the reference laboratory. This was calculated from the date the isolate was sent to the reference laboratory, to the date the result was entered electronically on our computer system (local laboratory turn-around time). Sixty-six isolates (77%) had sensitivity results available within 14 days of the candidaemia report. However, the reference laboratory had a shorter average turn-around time (calculated from date of receipt of specimen by reference laboratory to final verification of result by reference laboratory) of 6 days (IQR 3–7) for the same isolates (Figure 3). Three isolates had a reference laboratory turn around time of more than 2 weeks; one was a mixed culture requiring purification and two required further identification by molecular techniques.

All 90 isolates sent for susceptibility testing were sensitive to amphotericin B, and 80 (87%) were sensitive to fluconazole (Table 2). All *C. albicans* strains were sensitive to fluconazole compared to 78.2% (36/46) of non-*albicans Candida* strains. The fluconazole susceptibility rate for all *Candida* isolates tested was 93% for year 1, 87% for year 2, 92% for year 3 and 85% for year 4. Table 2 also



**Figure 3.** Turn-around times for local laboratory (final verification of results) compared to reference laboratory turn-around times.

shows the susceptibility profile of the isolates to itraconazole and flucytosine. The single isolate tested against caspofungin and voriconazole was susceptible.

## Treatment

Fourteen patients were already receiving antifungal treatment at the time the candidaemia was reported. Six patients died before the blood culture result, two were never treated and there were insufficient data on six patients. Eighty-four percent (54/64) of the remaining episodes achieved the audit target of commencing treatment within 24 h of a positive blood culture result and 63/64 episodes (98%) were started on antifungal treatment within 48 h. Treatment was started 15 days later in one case because the initial candidaemia was presumed to be due to contamination, but a subsequent repeat blood culture nine days later was again positive. Of the two untreated cases, one was an out-patient and survived, while the other patient died 42 days later (subsequent blood cultures on this patient were negative). Flucytosine was added as a second antifungal agent in five neonates and one adult. Two of the cases were complicated by endocarditis, and one had meningitis. Caspofungin was combined with amphotericin B in one case with disseminated skin and splenic lesions.

## Appropriateness of antifungal treatment

### Susceptibility

Of the eight patients with fluconazole intermediate/resistant strains, four were initially commenced on fluconazole. One patient was changed to amphotericin B the next day following the blood culture result, while another (terminally ill) patient had treatment withdrawn. Of the two surviving patients, one was transferred to another hospital on day 9 of fluconazole treatment before susceptibility data were available; the other was successfully discharged after 16 days of fluconazole (strain was of intermediate susceptibility to fluconazole). Fifty-six candidaemia episodes were associated with fluconazole-susceptible strains. On the basis of susceptibility results, 95% (61/64) of treated cases received optimum antifungal therapy (i.e. either amphotericin B, or fluconazole if susceptible).

### Duration

Eleven of the 92 episodes had incomplete data on duration of treatment. Of those with information available, six died prior to the blood culture result, two did not receive treatment, 23 died before completion of treatment and 14 died after the treatment course was completed. Thirty-six patients survived the treatment and were discharged successfully. The mean duration of treatment was 25.3

**Table 2** Susceptibility of candida isolates to fluconazole, itraconazole and flucytosine

Isolates	Fluconazole				Itraconazole				Flucytosine			
	Sensitive	Intermediate	Resistant	Not tested	Sensitive	Intermediate	Resistant	Not tested	Sensitive	Intermediate	Resistant	Not tested
<i>C. albicans</i>	44	0	0	0	44	0	0	0	42	0	2	0
<i>C. parapsilosis</i>	10	0	0	0	9	0	1	0	10	0	0	0
<i>C. glabrata</i>	19	1	3	0	3	8	12	0	22	1	0	0
<i>C. tropicalis</i>	4	0	1	0	5	0	0	0	5	0	0	0
<i>C. lusitanae</i>	2	0	0	0	1	0	0	1	1	0	0	1
<i>C. guilliermondi</i>	1	0	1	0	0	1	1	0	2	0	0	0
<i>C. krusei</i>	0	0	4	0	1	0	3	0	1	0	3	0
<i>Candida</i> sp.	0	0	0	5	0	0	0	5	0	0	0	5
Total	80	1	9	5	63	9	17	6	83	1	5	6

All isolates were sensitive to amphotericin B.

days (SD 14.4 days) among patients who died after completing treatment and 12.8 days (SD 11.7 days) among those who died before completing antifungal treatment. Among patients who survived or completed treatment before death, the mean duration of treatment was 24.5 days (SD 13.7 days); 81% received at least 2 weeks of antifungal therapy, 52.8% had at least 3 weeks of treatment and 33.9% had at least 4 weeks of treatment. However, only 5/11 cases had specific instructions on duration of antifungal therapy upon transfer to another hospital.

### Complications and outcome

There were two cases of retinitis, six cases of probable endocarditis and four confirmed cases of endocarditis (vegetations on echocardiography). Four patients had disseminated skin and splenic lesions (two identified only at post-mortem examination). The true incidence of these complications is likely to have been higher, because trans-thoracic echocardiography was performed in fewer than half of the episodes (44%) and ophthalmological examination was performed in only 16% of episodes. *Candida* was also isolated from intra-abdominal collections in six cases, from cerebrospinal fluid (CSF) in two cases and from pleural fluid in one patient.

The case fatality rate was 55.5% (50/90), with a 30-day mortality of 41.5%. The neonatal group had a higher 30-day mortality of 50%. Neonates born after 30/40 gestation survived beyond day 30 post candidaemia.

Age was an important predictor of survival. The median age of surviving patients was 41.5 years (IQR 4–68 years), compared to a median age of 61.5 years (IQR 41–78 years) for patients who died ( $p=0.0039$ ). When disease severity was adjusted for using the McCabe score, the effect of age was not statistically significant ( $p=0.196$ ). The McCabe score was an independent predictor of mortality, with an odds ratio of 18 (95% CI 4.8–67.9,  $p=0.0001$ ) associated with class 2 (ultimately fatal) and 3 (rapidly fatal) disease compared to class 1 (non-fatal underlying) disease.

There was no difference in mortality based on line colonization ( $p=0.912$ ) or the presence or absence of a line ( $p=0.2$ ). The patients who died had a longer interval before starting treatment compared with those who survived, with a difference of half a day between them but this did not achieve statistical significance.

There were too few patients with an abnormal echocardiogram to determine its effect on mortality. The majority of complications were among those

that died: those who died, 18.5% had complications, compared to a 5.3% complication rate for survivors ( $p=0.06$ ). Of the 12 cases with complications, 10 died, including 4 of the 6 who had endocarditis. After adjustment for age, the presence of complications was associated with an odds ratio for mortality of 6.5 (95% CI 1.2–36.5,  $p=0.03$ ).

## Discussion

In this study, the management of patients with candidaemia in Addenbrooke's Hospital was consistent with the proposed national standards of care for patients with invasive fungal infections.<sup>8</sup> The results of our audit confirm the importance of candidaemia as an increasingly important contributor to morbidity and mortality among hospitalized patients. There was a year-on-year increase in the number of candidaemia cases, but the number of cases with non-albicans *Candida* and the fluconazole susceptibility rate remained unchanged over this period. While this differs from some studies,<sup>5,6</sup> a constant epidemiology was also seen in some other studies.<sup>12,13</sup> The hierarchy of frequency of isolation of the different species is also similar to the findings of the SENTRY antimicrobial surveillance programme.<sup>14</sup> Mortality rates at 30 days were similar to studies in Ireland,<sup>15</sup> the US,<sup>12</sup> Europe,<sup>16</sup> and Spain<sup>17</sup> but higher than in Italy<sup>18</sup> and other studies from the UK.<sup>2,3</sup> The high mortality rate and the predominance of intensive care patients reflect the severity of the underlying disease in this group of patients. The demographic details of our patients are comparable to those in other studies.<sup>2,3,17–19</sup>

The presence of intravascular catheters remains a major predisposing factor for candidaemia. The removal of intravenous catheters has been associated with reduced mortality in both adults<sup>2,17,20,21</sup> and neonates.<sup>22</sup> Lines were removed promptly in the majority of episodes, but delays occurred, predominantly among non-ITU patients.

Neonatal intensive care patients were a high-risk group, particularly the low-birth-weight babies and infants born at <26 weeks gestation.<sup>23</sup> Forty percent of all *Candida parapsilosis* cases (4/10) occurred in the neonatal ICU group (neonatal cases account for only 8% of the patients in this audit). A survival rate of 75% was achieved in those infected with *Candida parapsilosis*, which is higher than other studies.<sup>24</sup>

This audit supports the use of the germ tube test for the initial identification of *C. albicans*, and suggests that it might be of value as an initial predictive marker for fluconazole susceptibility,

as all the *C. albicans* strains in this audit were susceptible to fluconazole. However, approximately 1–2% of *C. albicans* do not produce germ-tubes,<sup>25</sup> while misinterpretation of pseudomycelia as germ-tubes is expected in a small percentage of non-*C. albicans* isolates.<sup>26,27</sup> Resistance to fluconazole remains rare.<sup>2,17</sup> It was significant only in haematology patients receiving fluconazole prophylaxis in two prospective trials.<sup>2,16</sup> We had fewer patients with haematological malignancies, compared to the experience of other units.<sup>2</sup>

Laboratory results were promptly reported to the relevant clinicians. The initial choice of antifungal agent was appropriate for 95% of the treated episodes, when assessed against subsequent susceptibility results. Appropriate antifungal therapy is associated with improved survival.<sup>15,28</sup> Although our local turn-around time for susceptibility results is long, this was for printed reports, and clinically relevant results would have been phoned in as soon as they were received from the reference laboratory.

Caspofungin was used only once in the study period, and susceptibility data were only obtained for one isolate. It is a safe and generally well-tolerated drug with proven efficacy in the treatment of candidaemia.<sup>29</sup> A recent study suggested voriconazole was as effective as, but not superior to, amphotericin B deoxycholate followed by fluconazole.<sup>30</sup> Combination therapy with flucytosine was not frequently used, even in patients with complications. This was probably because of the high proportion of critically ill patients with a degree of renal impairment, and the need for monitoring blood concentrations of flucytosine.<sup>31</sup> Nevertheless, the use of flucytosine in combination treatment has potential advantages over amphotericin B or fluconazole monotherapy,<sup>32,33</sup> and is recommended in cases of severe candidaemia, particularly of the central nervous system, eye or cardiac valves.<sup>9,34</sup> More recently, the combination of amphotericin B and fluconazole has also been shown to be associated with improved success and more rapid clearance of candidaemia compared with fluconazole monotherapy, and may be preferable in more critically ill patients.<sup>35</sup> Of concern in this audit is the low rate of echocardiography and ophthalmology referral. Ophthalmic review was documented in only 16% of cases.

The IDSA recommends that candidaemia therapy should be continued for 2 weeks after the last positive blood culture result and resolution of signs and symptoms of infection.<sup>9</sup> The majority of patients in this audit (81%) received at least 2 weeks of therapy. However, the lack of proper treatment plans for inter-hospital transfers is of concern.

This audit was not an inclusive survey of all invasive candidiasis, as it was based on candidaemia isolates, and blood cultures have been reported to be negative in up to 50% of all autopsy-proven cases of invasive candidiasis.<sup>36</sup> Data were also missing, due to the retrospective nature of the study. We were unable to ascertain the attributable mortality. Furthermore, the role of new antifungals (e.g. caspofungin and voriconazole) has not been explored in this audit. We did not investigate the efficacy of azole prophylaxis, particularly among the neonatal and neutropenic groups, and the possible reasons for the unchanged fluconazole resistance rate noted in this audit. The role of other rapid identification tests for *Candida* and the cost-implications of providing a local identification and susceptibility service were also not evaluated. We hope that future audits will address these issues.

We recommend expanding current staff teaching sessions to include the care and management of intravascular catheters, particularly for clinical and nursing staff dealing with critically ill and immunosuppressed patients. Physicians also need to learn the importance of investigating for the presence of complications of candidaemia, because this will influence the duration and type of antifungal treatment, as well as affecting overall outcome. Communication also needs to be improved with regards to the inter-hospital transfer of patients.

Partly as a result of this audit, we have instituted a dedicated central venous catheter insertion team, in order to reduce the incidence of line-related infections<sup>37</sup> and therefore candidaemias. We have also started our own local identification and susceptibility testing of all *Candida* isolates from significant sites. Provision of this service locally would reduce the turn-around time, and would enable patients who were treated with expensive and potentially toxic agents (e.g. amphotericin B) to be switched to alternative agents.

## Conclusion

Candidaemia remains associated with a high mortality, despite appropriate antifungal agents given in a timely manner. Overall, the audit standards set by the BSMM and the IDSA were met, and discrepancies did not lead to a change in outcome. Further work is required to reduce the incidence of invasive candidiasis in high-risk patients. Improved intravenous catheter care and increased awareness of complications is required, while further studies of prophylaxis/pre-emptive therapy are necessary.

## Acknowledgements

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