Excess mortality, length of stay and cost attributable to candidaemia

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Summary  Background: There were 1967 reports of Candida species isolated from blood specimens in 2007 in the UK (excluding Scotland). Such infections are particularly common in the intensive care unit (ICU). The impact of candidaemia on mortality, length of stay (LOS) and cost in a UK hospital was examined.

Methods: A retrospective analysis of candidaemia episodes and appropriate matched controls was undertaken based on data from the ICU, high dependency units and hospital wards at Wythenshawe Hospital in Manchester. The study covered the period November 2003—February 2007.

Results: In total, 48 case-patients of candidaemia and 81 control-patients were identified. The attributable mortality due to candidaemia varied from 21.5% to 34.7%. Candidaemia patients spend on average 5.6 days more in the ICU than matched patients and generate mean additional costs of at least £8252 per patient, £16,595 in adults only.

Conclusion: Candidaemia remains a severe disease associated with high attributable mortality in the UK. In addition, candidaemia leads to additional ICU length of stay and costs. The implication is an attributable cost of at least £16.2 million with 683 deaths attributable to candidaemia per year in the UK.

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Introduction

Infections due to Candida species are common and Candida species are the predominant fungal nosocomial pathogens, especially in the intensive care unit (ICU).\textsuperscript{1,2} Data from the UK show that Candida species are the eighth most common cause of hospital-acquired bloodstream infections.\textsuperscript{2} A study at six UK hospitals\textsuperscript{3} found the rate of candidaemia to be more than 3 cases per 100,000 bed days while a recent prospective survey in Scotland reported an incidence rate of 4.8 cases per 100,000 population per year.\textsuperscript{5} The latest data from the Health Protection Agency indicate that a total of 1967 reports of Candida species were made in 2007 by laboratories in England, Wales and Northern Ireland (representing more than 90% of the UK population) confirming an increasing trend during the last decade.\textsuperscript{6} A recent retrospective study in our own ICU has shown that the incidence of candidaemia changed from 4.9/1000 ICU admissions in 2004—10.1 and 9.1/1000 ICU admissions in 2005 and 2006 respectively (unpublished). The rise in the incidence of candidaemia is due to many factors such as an increase in intensive care, greater use of invasive technologies, intravascular catheters and an increasing use of antibiotics.\textsuperscript{7}

Candidaemia has been shown to be associated with an increased length of hospital stay, higher mortality, and greater costs,\textsuperscript{8,9} although the number of studies capturing these types of data is limited.\textsuperscript{9} In a matched case-control study in the USA, the excess length of stay was 10.1 days in adults and 21.1 days in paediatric patients,\textsuperscript{10} and in a UK study, attributable 30-day mortality was reported as 26.4%.\textsuperscript{4}

How much excess mortality is really attributable to candidaemia remains a topic for debate.\textsuperscript{11} This is due to the underlying comorbidities and risk factors that generally characterise patients infected with Candida.\textsuperscript{11,7} Given that these patients will have a poor prognosis, it is often extremely difficult to discriminate between mortality attributable directly to the bloodstream infection and the mortality that is actually caused by the underlying condition.\textsuperscript{11,7}

Therefore we designed a matched case-control study based on data from our own hospital in order to estimate attributable mortality in addition to the impact of candidaemia on length of stay and costs due to an episode of candidaemia by comparing patients with candidaemia with hospitalised patients without candidaemia who were otherwise similar.

Methods

A retrospective analysis was undertaken of candidaemia in patients admitted to Wythenshawe Hospital between the 10th November 2003 and the 8th February 2007. The hospital’s audit committee approved the study.

Wythenshawe Hospital forms part of the University Hospital of South Manchester NHS Foundation Trust. It is an acute teaching trust, covering the geographical area of South Manchester, South Trafford, North East Cheshire and West Stockport. The population it serves is approximately 250,000. The Trust provides specialist services to the immediate catchment population, as well as services to patients from further afield as a tertiary referral centre for cystic fibrosis (~350 adult cases), heart and lung transplantation (approximately 40 transplants annually), burns, complex respiratory problems, and cardiothoracic surgery.

The general ICU at Wythenshawe has 9 beds and the cardiothoracic ICU also has 10 beds, with an additional 17 HDU beds. Patients who developed clinically and microbiologically documented candidaemia were identified through a microbiological laboratory survey and data were recorded in an electronic database. The patients chart review was performed in order to identify clinically relevant episodes.

Cases

Candidaemia was defined as at least one positive blood culture yielding Candida species in patients with fever or other signs of clinical infection.\textsuperscript{12} During the study period there were no changes in microbiological laboratory techniques. Candida species were isolated from blood using BacT/Alert system (bioMerieux, Basingstoke, UK). The species were identified using Microring YT (Medical wire UK), cornmeal agar (Oxoid Ltd., Basingstoke, UK), and Auxacolor2 (Biorad UK). A few isolates were sent to the Regional Mycology Laboratory, Manchester for confirmation of identification (utilising CHROMagar Candida) (M-Tech Diagnostics Ltd., Warrington, UK), Czapek Dox agar (Oxoid) and ID32C (bioMerieux) while all isolates were tested for antifungal susceptibility to fluconazole and fluucytosine.

Matching

Controls were matched for age (+/- 12 years), gender, month of admission (+/- 2 months), surgical operation, clinical diagnosis and severity at admission and hospitalisation on ward (ICU/non-ICU). In addition, the underlying disease was matched as closely as possible using these categories: GI surgery, burns, cardiac surgery, orthopaedic respiratory infections, other infections and renal failure (renal failure was defined by requirement for renal support). The intention was a 1:2 case: control match, but some matches were not found, and so only one match was used for these cases. Controls were identified using the wards’ admission books. GP did the case finding and matching, using the pre-specified criteria.

Closeness of matching

Controls were matched within +/− 12 years in age, although with some of the less common diagnoses this was >20 yrs (e.g. burns patients). Premature babies were matched as close to gestational age as possible. The transplant patients were matched to age and organ of transplant but not sex. Where diagnosis was not exactly the same, controls were found using categories already mentioned, taking into consideration similar existing co-morbidities.

Unit costs

ICU and High Dependency Unit (HDU) daily unit costs were based on a review of unit costs available in the literature. Mean values were calculated and used in the baseline analysis.
Statistical analysis

Fisher’s exact test was used for univariate analysis for continuous variables and the Wilcoxon non-parametric alternative when distributional assumptions were in doubt. A conditional logistic regression analysis was used for matched case-control groups in order to relate the dichotomous dependent variable, in-hospital mortality, to independent variables such as the existence or not of candidaemia, age and whether the patient had received ICU care.

Multiple regression analysis was used to estimate attributable length of stay and hospital cost based on the application of the derived daily unit costs for ICU and HDU. No data were available concerning the length of stay in the hospital ward after being transferred from the ICU and/or HDU hence it was impossible to include the cost due to the hospital ward length of stay. Statistical significance was defined as a p value of less than 0.05. The results were analysed using the statistical package STATA (StataCorp, TX, USA).

Results

There were a total of 48 cases and 81 controls when considering all patients. Approximately 1/3 of patients were over 70 years of age and five (10%) were premature infants. In the case of ICU patients the number of cases and controls was 40 and 68 respectively. The most common species was Candida albicans (32–66.7%) followed by Candida glabrata (7–14.6%). In five cases, multiple species types were identified. Key demographic details of cases (Candida albicans — 25 (62.5%) and Candida glabrata — 6 (15.0%)) and controls are shown in Table 1. The most common antifungal therapy administered was fluconazole (47.9%) with a mean initial daily dose of 317 mg followed by caspofungin (25%) with a mean initial daily dose of 63.3 mg. No antifungal therapy, if given at least 48 h before blood culture, age and whether antifungal treatment, if given at least 48 h before blood culture, was administered were considered in the modelling but turns positive, and whether antifungal treatment if given at least 48 h before blood culture was administered were considered in the modelling but was not collected for control patients.

The overall mortality rate attributable to candidaemia was calculated to be 34.7% in the case of all patients and 28.3% in the case of ICU patients (Table 2). Four of the eight (50%) patients with candidaemia not admitted to the ICU died compared with none of 27 matched patients, an attributable mortality of 50%. Overall, 19 of 22 candidaemia patients died within 30 days of the development of candidaemia.

When the analysis was limited to adult patients (defined as those ≥ 16 years old), the attributable mortality was reduced to 30.6% (41.9% vs. 11.3%) for all patients (OR = 7.0 (2.0–24.3)) and 21.5% (38.9% vs. 17.4%) for ICU patients (OR = 3.0 (0.8–11.6)).

The mean duration of ICU LOS for case-patients was 17.8 days (median = 13 days and range [0–76]) and for control-patients the corresponding figures were 12.2 days (median = 2 days and range [0–103]) (p = 0.006) indicating a mean attributable increase of 5.6 days due to candidaemia (Table 3). When the analysis was restricted to surviving matched pairs (i.e. at least one surviving control for each surviving case) the mean duration of ICU LOS for case-patients was 18.7 days (median = 14 days and range [0–63]) and for control-patients the corresponding figures were 6.6 days (median = 1 days and range [0–42]) (p = 0.002) indicating a mean attributable increase of 12.1 days in either ICU. In the case of HDU LOS there were no statistically significant differences for all patients (2.9 vs. 3.3 days for cases and controls respectively) or HDU or both due to candidaemia. For surviving matched pairs (2.4 vs. 4.0 days for cases and controls respectively).

From our regression analysis (Table 4) we were able to calculate coefficients for a simple model in order to estimate the attributable ICU LOS based on candidaemia status, age and HDU LOS. Factors such as timing of antifungal therapy, if given at least 48 h before blood cultures turned positive, and whether antifungal treatment was administered were considered in the modelling but were discarded due to lack of significance. For a candidaemia patient with a mean age of 54 years and a HDU LOS of 3.1 days (mean LOS in HDU of the whole dataset) the estimated ICU LOS was 18.8 days. For babies (<1 year), the estimated mean ICU LOS was 38.8 days and for a 75 year old the mean LOS was 11.1 days.

| Table 1 Number of matched sets and demographics of case and control patients. |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Description of matched sets       | All patients    | Control-patients | ICU patients    | Control-patients |
| Sets with 2 control-patients      | 33 (69%)        | 66              | 28 (70%)        | 56              |
| Sets with 1 control-patient       | 15 (31%)        | 15              | 12 (30%)        | 12              |
| Total                             | 48              | 81              | 40              | 68              |
| Male:Female                       | 61.5:38.5       | 65.4:34.6       | 60.0:40.0       | 63.2:36.8       |
| Mean age (range)                  | 53.8 [0, 89]    | 54.3 [0, 92]    | 51.9 [0, 89]    | 53.3 [0, 87]    |
| <1 year                           | 5 (10.4%)       | 9 (11.1%)       | 4 (10.0%)       | 8 (11.8%)       |
| 1–15 years                        | 0 (0.0%)        | 1 (1.2%)        | 0 (0.0%)        | 0 (0.0%)        |
| 16–29 y                           | 5 (10.4%)       | 2 (2.5%)        | 5 (12.5%)       | 2 (2.9%)        |
| 30–49 y                           | 6 (12.5%)       | 13 (16.1%)      | 6 (15.0%)       | 12 (17.7%)      |
| 50–59 y                           | 8 (16.7%)       | 14 (17.3%)      | 7 (17.5%)       | 13 (19.1%)      |
| 60–69 y                           | 8 (16.7%)       | 14 (17.3%)      | 6 (15.0%)       | 11 (16.2%)      |
| ≥70 y                             | 16 (33.3%)      | 28 (34.6%)      | 12 (30.0%)      | 22 (32.4%)      |
| Total                             | 48              | 81              | 40              | 68              |
Another multiple regression analysis was undertaken in order to determine those variables which explain the difference in cost. Costs of care for case and control patients were approximated using the daily cost of ICU and HDU (£1509 and £756 respectively). In a secondary analysis, we attempted to estimate the additional cost attributable to case patients taking into account differences in mean age for cases and controls. For all patients, the mean additional costs for case-patients were £8252 compared with control-patients. For adult patients alone, the difference was greater, £16,595. These cost differences were statistically significant using the Wilcoxon rank-sum test.

Estimated total cost = 25,192 + 12,033 AFT + 23,440 ICU – 427 AgeOA.

where AFT = Antifungal therapy (yes or no); ICU = Treated in ICU (yes or no); AgeOA = Age on Admission.

In a secondary analysis, we attempted to estimate the additional cost attributable to case patients taking into account differences in mean age for cases and controls. For all patients, the mean additional costs for case-patients and control-patients were £8252 compared with control-patients. For adult patients alone, the difference was greater, £16,595. These cost differences were statistically significant using the Wilcoxon rank-sum test.

### Discussion

The main findings of our case-control study during the period 2004–2006 are that significant mortality and costs are attributable to candidaemia when matched with comparable non-candidaemia patients. This higher attributable mortality applies to all patients and those who received care in the ICU. These results are consistent with the conclusions of most published studies and a systematic review of matched cohort and case-control studies. In our study, the attributable mortality was reduced when the analysis was limited to adult patients. The majority of patients in our study were from the ICU, this is in contrast to the results from other published case-control studies that tend to concentrate on hospital patients in general. Attributable mortality for such patients ranges from 10.1% (paediatric patients) to 49%. The lower mortality observed in these trials may be due to the exclusion of certain patients with candidaemia, because of inclusion or exclusion criteria or ease of obtaining consent. Different case-control study populations vary widely in size.

On the other hand, certain researchers have proposed that the mortality attributable to candidaemia is not significant in patients with an already high-expectation mortality. In one study, the authors concluded that nosocomial candidaemia in ICU patients does not adversely affect the outcome. In contrast, in others studies nosocomial candidaemia is associated with high crude and attributable mortality which is consistent with our study. Many factors could explain this disparity, but underlying severity of illness is likely to be a major explanatory factor.

Our study also suggests that the mean length of stay in the ICU was longer for all candidaemia patients and for all surviving candidaemia matched pairs. In the study by Zaoutis, et al. (hospital patients) the difference for all adult patients was 11.1 days. In another study, the difference between cases and controls was extended when the analysis was limited to survivors (10.5 days vs. 3 days) as in this study although these results were derived from all hospital patients. In possibly a more directly comparable study, Blot considered the effects of nosocomial candidaemia on outcomes of critically ill patients. With 73 cases and 146 controls, the mean length of stay in the ICU for candidaemia patients was 36 ± 33 days compared with 25 ± 23 for controls. The reason for this extended LOS is subject to debate although most authors cite the severity of the disease with the high probability of complications requiring further hospitalisation.

These findings highlight the importance of the most appropriate treatment of candidaemia for individuals as well as the NHS given the impact on LOS, costs and mortality and the relevance of subjecting new treatments to economic evaluations in which both clinical and economic outcomes are considered. Cost-effectiveness

### Table 2: Univariate analysis of mortality among case and control patients.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>ICU patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude mortality</td>
<td>OR (CI95)</td>
</tr>
<tr>
<td>Overall</td>
<td>22/48 (45.8%)</td>
<td>9.1 (2.7–31.0)</td>
</tr>
</tbody>
</table>

OR = Odds ratio; CI95 = 95% confidence interval.

### Table 3: Multivariate analysis of mortality for case and control-patients.

<table>
<thead>
<tr>
<th></th>
<th>OR (CI95)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-patient</td>
<td>15.7 (2.9–84.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age group 30–49</td>
<td>6.0 (0.2–197.6)</td>
<td>0.314</td>
</tr>
<tr>
<td>Age group 50–59</td>
<td>36.9 (0.6–2375)</td>
<td>0.089</td>
</tr>
<tr>
<td>Age group 60–69</td>
<td>22.5 (0.2–2442)</td>
<td>0.193</td>
</tr>
<tr>
<td>Age group ≥ 70</td>
<td>21.8 (0.01–41811)</td>
<td>0.424</td>
</tr>
<tr>
<td>Received ICU care</td>
<td>3.4 (0.3–39.9)</td>
<td>0.338</td>
</tr>
</tbody>
</table>

### Table 4: Estimation of ICU length of stay (days) using multiple regression analysis.

<table>
<thead>
<tr>
<th></th>
<th>Coefficient CI95</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-patient</td>
<td>6.54 –0.33;12.75</td>
<td>0.039</td>
</tr>
<tr>
<td>All ages</td>
<td>−0.37 –0.49;−0.25</td>
<td>0.000 a</td>
</tr>
<tr>
<td>HDU LOS</td>
<td>0.48 –0.17;0.78</td>
<td>0.003</td>
</tr>
<tr>
<td>Constant term (intercept)</td>
<td>30.79 23.29;38.28</td>
<td>0.000 b</td>
</tr>
</tbody>
</table>

a Smaller than 0.00005.

b Smaller than 0.0005.
analysis would be the appropriate form for those interventions that are likely to reduce mortality whilst cost minimisation would be the most likely form of evaluation for those interventions considered likely to reduce ICU LOS.

There are a number of limitations to our study. Clearly, given the nature of candidaemia and retrospective studies in general care must be taken if inferences about causality are to be made. It would most likely be an oversimplification to assume that all the difference in mortality that was observed in our dataset can be directly attributable to candidaemia. This is due to the fact that in no study is it possible to match for all factors that may influence mortality.

Costs were also limited to ICU and HDU since other resources such as length of stay in the hospital ward were not recorded in the original database. However, it is unlikely that the difference in costs due to hospital ward LOS would be greater than the difference in costs attributable to the combined ICU and HDU LOS. Additionally, mean unit costs were used given the difficulty of obtaining marginal costs, this is a problem with the majority of studies of an economic nature. However, if the use of these resources could be reduced although it might not actually reduce NHS costs it would imply that more resources (hospital and ICU bed days and staff time) could be reallocated to other disease areas. Our study is limited to one centre and a modest population although by no means is it the smallest when considering similar studies. In fact, the size of previously published case-control candidaemia study populations has varied widely from 26 cases and 52 controls to 10,067 cases and 19,329 controls. Accepting these limitations, our study has provided further evidence that candidaemia both in the hospital setting and the ICU is almost certainly associated with an increase in mortality and costs.

The study also generates new questions that can only be answered by further research such as the impact on mortality and costs of specific Candida species and the use of prospective studies to address this type of question. Candidaemia represents a significant healthcare burden in terms of hospitalisation, mortality and costs. When these figures are applied to the annual incidence figures collected for England, Wales and Northern Ireland the implication is an attributable cost of at least £16.2 million with up to 683 deaths attributable to candidaemia per year. The attributable costs and mortality observed in this study indicate the need to identify and implement more effective health care strategies involving both prevention and treatment measures that will have an impact on mortality and the costs of candidaemia.

Acknowledgement

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Conflict of interest

Ibrahim Hassan and Georgina Powell report no conflict of interest. Manpreet Sidhu is an employee of Astellas Pharma Ltd and Warran Hart an employee of Ecostat Consulting Ltd which was commissioned by Astellas to assist in analysis and writing of this study. In the past 5 years, David Denning reports having received grant support from Astellas, Merck, Pfizer, F2G, OrthoBiotec, Indevus, Basilea, the Fungal Research Trust, the Wellcome Trust, the Moulton Trust, The Medical Research Council, The Chronic Granulomatous Disease Research Trust, The National Institute of Allergy and Infectious Diseases and the European Union. He has been an advisor/consultant to Basilea, Vicuron (now Pfizer), Pfizer, Schering Plough, Indevus, F2G, Nektar, Dalichi, Sigma Tau, Astellas, Gilead and York Pharma. He has been paid for talks on behalf of Schering, Astellas, Merck, GSK, Chiron, AstraZeneca, Myconostica and Pfizer. He holds founder shares in F2G Ltd and Myconostica Ltd, both University of Manchester spin-out companies.

References


