

1 **Letter to the Editor**

2 **Impact of a candidaemia care bundle on patient care at a large teaching hospital in**  
3 **England**

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5 **Running Title:** Care bundle for candidaemia

6 **Key words:** candidaemia; management; antifungal stewardship; care bundles

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20 **Dear Editor,**

21 Fortún and colleagues, in this Journal, compared candidaemias in two 5-year periods (2000-  
22 2004 and 2005-2009) in a single institution.<sup>1</sup> They observed a significant increase in the  
23 number of cases per 1000 admissions per year between study periods: in the first period,  
24 *Candida albicans* was the most frequently isolated species (42%), followed by *Candida*  
25 *parapsilosis* (34%) and *Candida glabrata* (13%). In the second period, episodes were  
26 associated with higher comorbidity and were more commonly nosocomial, with a more  
27 frequent catheter-related source and an increased rate of *C. glabrata* infection. Their  
28 mortality remained the same (37% at one month).

29

30 We similarly reported a 30-day mortality of 40% in 2006.<sup>2</sup> Since then we have instituted a  
31 number of interventions including in-house identification and susceptibility testing, use of  
32 echinocandins as empirical therapy, and the introduction of an antifungal stewardship (AFS)  
33 team comprised of a consultant microbiologist and antimicrobial pharmacist in July 2013.<sup>3</sup>  
34 Part of the role of the AFS team included the introduction of a candidaemia care bundle  
35 which involves the clinical review of six elements of care: commencement of an antifungal  
36 agent on the same day as the microscopy result is reported; removal of central venous  
37 catheters (CVC) within four days of candidaemia onset in non-neutropenic patients; sending  
38 repeat blood cultures; performing echocardiography; ophthalmology review; and  
39 subsequent rationalisation of therapy on the same day as susceptibility results become  
40 available. These were chosen in line with the Infectious Diseases Society of America  
41 guidelines on the management of candidaemias.<sup>4</sup> We compared the management and

42 outcomes of patients with candidaemias prior to and after the implementation of the AFS  
43 programme.

44

45 The evaluation was conducted at Cambridge University Hospitals NHS Foundation Trust  
46 (CUH), a large, single-site, tertiary teaching hospital in the East of England with 1,100 beds,  
47 70,000 inpatient admissions and 170,000 total admissions per annum. The hospital offers a  
48 number of specialist services, including solid organ transplantation (multivisceral, liver, renal  
49 and pancreas transplants), haematology/oncology (including stem cell transplantation) and  
50 neurosurgery.

51

52 All patients (adult and paediatric) with first episode of *Candida* spp. bloodstream infection  
53 during the study period were included in the study. Patients who died prior to blood  
54 cultures becoming positive were excluded from the analysis. The primary team responsible  
55 for patient care routinely received phone advice on management from a clinical  
56 microbiologist following a positive blood culture result. In addition, patients in the post-  
57 intervention group were reviewed by the AFS team. Data was obtained retrospectively for  
58 the pre-intervention group and prospectively in the post-intervention group and included  
59 compliance with all six elements of care as outlined earlier, markers of clinical severity at  
60 baseline (Charlson comorbidity index, CCI) and 30-day mortality. Statistical analysis was  
61 performed using the two-tailed Fisher's exact test for categorical variables and Mann  
62 Whitney U test for continuous variables on IBM SPSS Statistics v20 software programme

63 (IBM, New York, USA). The study was registered with the CUH audit department and did not  
64 require ethical approval.

65

66 There were 47 candidaemia episodes in 2009-2010 and 33 episodes in 2013-2014 (Table 1).  
67 The proportion of candidaemia due to *C. albicans* fell from 48% in 2009-10 to 39% in 2013-  
68 14 ( $p=0.34$ ). Three patients with candidaemia from 2009-10 were excluded from further  
69 analysis due to death occurring prior to blood cultures becoming positive. The baseline age  
70 and severity of illness did not differ significantly between the two periods (median CCI 3 in  
71 2009-10 versus 4 in 2013-14;  $p=0.52$ ).

72

73 The implementation of the AFS programme led to improved compliance with all elements of  
74 the care bundle: initiation of effective treatment on the day of the positive microscopy  
75 result (94% versus 93%;  $p=1.00$ ), follow up blood cultures (100% versus 93%;  $p=0.26$ ), timely  
76 removal of CVC (91% versus 65%;  $p=0.03$ ), ophthalmology review (100% versus 64%;  
77  $p<0.01$ ) and echocardiography (100% versus 88%;  $p=0.06$ ). There was a higher rate of timely  
78 rationalisation of antifungal therapy (83% versus 43%;  $p=0.02$ ) and a trend towards  
79 improved 30-day mortality (9% versus 27%;  $p=0.08$ ). Initial clinical review lasted  
80 approximately 10 minutes and follow-up review a further 10 minutes to confirm that all the  
81 actions had been performed.

82

83 The rise in the proportion of non-albicans *Candida* has been described previously,<sup>1</sup> but  
84 whilst they reported a rise in the number of candidaemias over time, we found a (non-

85 significant) fall, similar to that described by Cleveland and colleagues.<sup>5</sup> They suggested this  
86 could be due to improved practice in the care of patients with CVC; our institution, along  
87 with other English hospitals has seen a fall in CVC-related bloodstream infections in recent  
88 years.<sup>6</sup>

89

90 Whilst a number of studies have described individual elements of the care bundle being  
91 associated with improved mortality (e.g. CVC removal and echinocandin use), only three  
92 studies have described care bundles for candidaemia previously. Antworth and colleagues<sup>7</sup>  
93 describe a single-centre before-after study comparing 37 patients (pre-intervention) with 41  
94 patients (post-intervention) and found improvements in care. Reed and colleagues<sup>8</sup> describe  
95 a single-centre before-after study comparing 85 (pre-intervention) and 88 patients (post  
96 intervention). Time to effective therapy was significantly shorter and therapy was  
97 administered to more patients in the post-intervention group (88% versus 99%;  $p=0.008$ )  
98 but they found no significant difference in in-hospital mortality (19% versus 30%;  $p=0.11$ ),  
99 infection-related length of stay or hospital costs during candidaemia. Takesue and  
100 colleagues<sup>9</sup> describe a multicentre study involving 608 patients in order to assess if  
101 compliance with the bundle improved mortality. They found a significant difference in  
102 clinical success between patients with and without compliance (92.9% versus 75.8%;  
103  $p<0.01$ ). Compliance with the bundles, however, was poor overall and failed to be an  
104 independent factor associated with favourable outcomes. Completion of all elements of the  
105 bundle in our study increased from 29% (12/42) pre-intervention to 87% (27/31) post-  
106 intervention ( $p<0.01$ ).

107

108 We acknowledge that this is a small single centre study but we believe that the  
109 implementation of the new candidaemia care bundle as part of the AFS programme was  
110 effective in improving compliance with standards of patient care, and led to targeted and  
111 more cost effective antifungal therapy and an overall improvement in clinical outcome, with  
112 minimal time (approximately one hour per month) and financial investment.

113

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115 **Transparency declarations:** T. G. is a Wellcome Trust clinical research training fellow. C. M.  
116 has received funding to attend conferences from Astellas, Pfizer and Gilead and an  
117 educational grant from Pfizer. S. H. A. has served on UK Advisory Boards for Gilead and MSD  
118 and has received sponsorship to attend international meetings from Schering-Plough, Gilead  
119 and Wyeth. D. A. E. has received funding to attend conferences from MSD, Gilead and  
120 Astellas.

121 H. Y. and K. K. – no conflicts of interest.

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**Table 1: Comparative descriptive analysis of candidaemia cases in the two study periods**

<b>Demographics</b>	<b>2009-2010 n=44</b>	<b>2013-2014 n=33</b>	<b>p-value</b>
Age, median (interquartile range)	64 (47 – 72.5)	56 (39-75)	0.40
Range	15-96	0 – 84	
Male	26 (59%)	15 (46%)	0.26
<b>Care bundle</b>			
Adequate empirical therapy	41/42* (98%)	32/32** (100%)	0.57
Effective empirical therapy commenced same day as positive microscopy	39/42* (93%)	30/32** (94%)	1.00
Removal of CVC in non-neutropenic patients within 4 days of candidaemia onset	20/31 (65%)	21/23 (91%)	0.03
Follow up blood cultures for clearance	41 (93%)	33 (100%)	0.26
Ophthalmology review	27/42* (64%)	33 (100%)	<0.01
Echocardiography	37/42* (88%)	33 (100%)	0.06
De-escalation to fluconazole ***	9/21 (43%)	15/18 (83%)	0.02
All elements of the bundle completed	12/42* (29%)	27/31** (87%)	<0.01
<b>Severity</b>			
Charlson co-morbidity score, median (interquartile range)	3 (2-5)	4 (2-6)	0.52
<b>Outcome</b>			
Death at 1 month	12 (27%)	3 (9%)	0.08
<b>Empirical treatment</b>			
Echinocandin	30 (65%)	25 (76%)	0.35
Fluconazole	5 (10%)	5 (15%)	0.45
Liposomal amphotericin B	7 (15%)	2 (6%)	0.16



<b>Microbiology</b>	<b>n=47</b>	<b>n=33</b>	
<i>C. albicans</i>	22 (48%)	13 (39%)	0.34
<i>C. glabrata</i>	17 (37%)	14 (42%)	0.37
Other <i>Candida</i> spp.	8 (17%)	6 (18%)	0.56

156

157 CVC: central venous catheter.

158 \*2 patients not treated due to palliation

159 \*\* missing data

160 \*\*\*Excluded 23 patients from 2009-10 and 15 patients from 2013-4 for the following reasons:

161 fluconazole-resistant isolate, fluconazole allergy, delay in obtaining susceptibility results, fluconazole

162 used as empirical therapy, patients not treated.