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Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive *Candida* species infections

Michael D. Parkins[1], Deana M. Sabuda[1], Sameer Elsayed[2–4] and Kevin B. Laupland[1–3,5,6]*

[1]Department of Medicine, Calgary Health Region and University of Calgary, Calgary, Alberta, Canada; [2]Department of Pathology and Laboratory Medicine, Calgary Health Region and University of Calgary, Calgary, Alberta, Canada; [3]The Center for Anti-Microbial Resistance, Calgary Health Region, University of Calgary and Calgary Laboratory Services, Calgary, Alberta, Canada; [4]Division of Microbiology, Calgary Laboratory Services, Calgary, Alberta, Canada; [5]Department of Critical Care Medicine, Calgary Health Region and University of Calgary, Calgary, Alberta, Canada; [6]Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

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***Objectives*: Although inadequate antimicrobial therapy has been demonstrated in multiple studies to increase the risk for death in bacterial infections, few data investigating the effect of antifungal therapy on outcome of serious fungal disease are available. We sought to assess the adequacy of empirical therapy and its effect on mortality in invasive *Candida* species infections.**

***Methods*: Population-based surveillance of all patients with *Candida* spp. cultured from blood and/or cerebrospinal fluid was conducted. Adequacy of empirical therapy was assessed according to published guidelines.**

***Results*: During a 5 year period, 207 patients had an invasive *Candida* spp. infection identified; in 199 cases (96%) adequate data were available for assessment of treatment and outcome at hospital discharge. One hundred and three (52%) cases were due to *Candida albicans*, 44 (22%) were due to *Candida glabrata* and the remainder were due to other species. Between the time of culture draw and reporting of a positive culture, only 64 (32%) patients were treated with empirical therapy; this was deemed adequate in 51 (26%). Patients who received adequate empirical therapy had a significant decrease in crude mortality [14/51 (27%) versus 68/148 (46%); risk ratio 0.60 (95% confidence interval 0.37–0.96); $P = 0.02$]. After adjusting for age and the need for intensive care unit admission in logistic regression analysis, the use of adequate empirical therapy was independently associated with a reduced risk for death [odds ratio 0.46 (95% confidence interval 0.22–1.00); $P = 0.05$].**

***Conclusions*: Adequate empirical therapy is used in a minority of patients with invasive *Candida* spp. infections but is associated with improved survival.**

Keywords: timing, delay, treatment, candidaemia, mortality

Introduction

Candida species are among the most common causes of nosocomial bloodstream infection.[1] Furthermore, invasive candidiasis is increasingly commonplace owing to the increasing use of intravascular catheters, broad-spectrum antibacterial agents and enhanced immunosuppression. In addition to an attributable mortality of 40–49%,[2–5] invasive candidiasis is associated with increased length of stay[6,7] and increased healthcare expenditure.[8,9] Risk factors for invasive candidiasis and mortality secondary to invasive candidiasis are well described.[2,4,5] An increase in the proportion of non-*albicans* isolates with reduced fluconazole susceptibility has prompted a shift from fluconazole as first-line therapy, for fear of therapeutic failure.[10–13] Fortunately, the choices available to treat invasive candidiasis have expanded in the last decade and include new azoles, echinocandins and amphotericin B lipid formulations.

Although inadequate empirical antibacterial therapies have long been recognized as an independent predictor of in-hospital mortality, few studies have specifically investigated the importance of timing of antifungal therapies with invasive

*Corresponding author. Tel: +1-403-770-3346; Fax: +1-403-770-3347; E-mail: kevin.laupland@calgaryhealthregion.ca

candidiasis.[14–19] While these reports have indicated that inadequate or delayed antifungal therapy is associated with an adverse outcome, many have been limited by a small sample size or have relied on species-predicted susceptibilities in defining adequacy of therapy.[18,19] There is often a significant delay in diagnosis of invasive candidiasis as the clinical presentation is non-specific and time for culturing is required. Accordingly, many experts advocate early empirical antifungal therapies in patients deemed high risk.[2,20,21] However, no studies to date have specifically addressed the role of empirical antifungal therapies on patient outcome. The objective of this study was to identify factors associated with receipt of adequate empirical antifungal therapy and assess its impact on mortality in a large population-based cohort of patients with invasive candidiasis.

Patients and methods

Patient population

All patients within the Calgary Health Region (population 1.2 million) with culture-proven invasive *Candida* spp. infection between July 1999 and June 2004 were identified using a centralized laboratory database as previously described.[22] Clinical, demographic and microbiological information for these patients was collected through an electronic linkage with associated databases. Only first episodes of invasive candidiasis were reviewed. Antifungal treatment regimens were identified by reviewing one central pharmacy database for each of the major acute care facilities (three adult hospitals and one paediatric hospital) in the region. No information on outpatient therapies was available for review. The antifungal drugs available for clinical use changed during the course of the study with the formulary addition of liposomal amphotericin B in January 2000 and of caspofungin in November 2003. Voriconazole was not available until after completion of the study. This study received ethical approval by the Calgary Health Region and the University of Calgary Ethics Review Board.

Definitions

All definitions were created *a priori*. Invasive *Candida* spp. infections were defined as isolation of *Candida* spp. from blood or cerebrospinal fluid (CSF). Infection was defined as community onset if the organism was isolated within 48 h from initial hospitalization and could not be attributed to a prior hospitalization. Death was defined as all-cause mortality during hospitalization. Adequacy of therapy was defined as per recent clinical practice guidelines.[21] Inadequate therapy was defined by the initiation of an agent to which the organism was found to be resistant on the basis of *in vitro* susceptibility,[23] the use of fluconazole for *Candida krusei*, or inadequate dosing. For the 21 (11%) isolates where antifungal susceptibility testing results were not available, adequacy of therapy was adjudicated based on typical species-specific resistance patterns.[2] Adequate daily dosing was defined as fluconazole $\geq$400 mg or $\geq$6 mg/kg intravenous (iv) or oral, amphotericin B deoxycholate $\geq$0.6 mg/kg iv, liposomal amphotericin B $\geq$3 mg/kg, and caspofungin 50 mg iv following loading dose of 70 mg. A fluconazole dose of 200 mg/day was considered adequate for patients who had both renal failure and fluconazole-susceptible isolates. Where information was not available, adult patients were presumed to be 70 kg and have normal renal function.

Empirical therapy was defined as receipt of any systemic antifungal regimen (AFR) prior to first reporting of positive blood culture results. Time to therapy was defined as the time from culturing the patient to the patient's receipt of anti-*Candida* therapy. Time to adequate overall therapy was defined as time from culturing to first administration of an antifungal drug to which the organism was fully susceptible. Antifungal prophylaxis was defined as receipt of systemic antifungal therapy for $\geq$24 h prior to cultures being drawn.

Statistical analysis

Individual variables were assessed using histograms prior to analysis to identify their underlying distribution. Variables with normal or near normal distributions were described with means and standard deviations (SD) and compared using the Student *t*-test. Medians with inter-quartile ranges (IQR) were used to describe non-normally distributed variables and compared using the Mann–Whitney *U*-test. Categorical variables were compared using the Fisher's exact test. Risk ratios (RR) were calculated by dividing the proportion with a given factor as opposed to without the factor and are reported with 95% confidence intervals (CI) calculated using the Woolf approximation. A logistic regression model was developed to determine independent factors associated with mortality. All factors associated with death in univariate analyses ($P \leq 0.2$) were initially included and backward stepwise variable elimination was used to develop the most efficient model. Calibration of the final model was assessed using the Hosmer-Lemeshow goodness of fit test and discrimination was assessed using the area under the receiver operator characteristic curve. Model results are reported as odds ratios (OR) with 95% CI. A two-sided *P* value of $\leq$0.05 was considered significant for all comparisons. All statistical analyses were performed using Stata version 9.0 (Stata Corp., College Station, TX, USA).

Results

Patient characteristics

During the 5 year time period, there were 207 patients with invasive candidiasis. Detailed clinical, treatment and outcome information was available for 199 patients (96%) and, unless otherwise indicated, comprises the study cohort. The median age was 58.6 (IQR 40.4–73.1); however, 29 (15%) were children and 11 (6%) were premature infants. Males accounted for 103 (52%) of the cohort. Co-morbidities were as follows: 26 (13%) chronic renal failure (CRF) [of whom 10 (5%) required intermittent haemodialysis], 6 (3%) stroke, 59 (30%) heart disease, 16 (8%) chronic obstructive lung disease, 36 (18%) diabetes mellitus, and 4 (2%) rheumatoid arthritis. No patients in the study were HIV positive. Sixty-six patients (33%) had underlying malignancies; 21 (11%) leukaemia, 5 (3%) lymphoma, 3 (2%) multiple myeloma and 37 (19%) solid organ malignancies. Five patients (3%) had received a stem-cell transplant and 8 (4%) had a solid organ transplant. Median length of hospital stay (LOS) was 32 days (IQR 16–60).

Microbiological characteristics

Candida albicans was the most common agent of invasive candidiasis accounting for 103 cases (52%), followed by *Candida glabrata* 44 (22%), *Candida parapsilosis* 12 (6%), *Candida tropicalis* 12 (6%), *C. krusei* 10 (5%), *Candida lusitaniae* 1 (0.5%), *Candida guilliermondii* 1 (0.5%) and non-*albicans* *Candida* spp. not otherwise speciated 16 (8%). *Candida* isolates

were from blood in 188 patients (94%), 9 patients had *Candida* isolated from CSF (5%) and 2 (1%) patients had positive cultures from both blood and CSF. There was no difference in site of infection ($P = 0.09$), *Candida* spp. ($P = 0.4$) or fluconazole susceptibility ($P = 0.14$) in those patients that received empirical AFRs relative to those that did not. The mean time from culture draw to first reporting of yeast was 2.4 (SD = 1.28) days. Antifungal susceptibility testing was performed on 178/199 isolates (89%). Pooled data indicated that 123/178 isolates (69%) were susceptible to fluconazole, 104/178 (58.4%) were susceptible to itraconazole, 177/178 (99%) were susceptible to amphotericin B deoxycholate, 175/178 (98%) were susceptible to voriconazole and 176/178 (99%) were susceptible to caspofungin. In the 21 (11%) instances when antifungal susceptibility results were not available, susceptibilities were predicted based on species.

Antifungal therapies

Antifungal therapies were used in 165/199 inpatients (83%) for a median in-hospital duration of 12.7 days (IQR 5.1–24.3). The median time to first antifungal therapy was 2.13 days (IQR 0.93–3.19) after culture draw. Overall, patients experienced a number of different AFRs with respect to drug and dose; 165 (83%) ≥ 1 AFR, 115 (58%) ≥ 2 AFR, 60 (30%) ≥ 3 AFR, 38 (19%) ≥ 4 AFR, 18 (9%) ≥ 5 AFR, 11 (6%) ≥ 6 AFR and 4 (2%) ≥ 7 AFR. During the study, the total days of drug therapy included; 1986 for fluconazole, 1008 for amphotericin B, 356 for liposomal amphotericin B, 87 for 5-flucytosine, 58 for caspofungin and 17 for itraconazole.

Empirical therapy was used in only 64 patients (32%). Patients with leukaemia [13/21 (62%) versus 51/178 (29%); RR 2.16 (CI 1.44–3.25); $P = 0.005$], a stem cell transplant [5/5 (100%) versus 59/194 (32%); RR 3.29 (CI 2.66–4.07); $P = 0.003$] and absence of COPD [1/16 (6%) versus 63/183 (34%); RR 0.18 (CI 0.03–1.22); $P = 0.02$] were more likely to receive any empirical therapy. Empirical therapies included fluconazole in 41 patients (64%), amphotericin B in 22 patients (34%) and caspofungin in 1 patient (2%). Patients treated empirically were more likely to have received prophylaxis [10/10 (100%) versus 54/189 (29%); RR 3.50 (CI 2.79–4.38); $P < 0.001$], adequate therapy overall [58/146 (40%) versus 6/53 (11%); RR 3.51 (CI 1.61–7.65); $P < 0.001$] and to have a longer in-hospital treatment duration [median 23.3 days (IQR 12.8–40.8) versus 12.6 (IQR 2.7–20.2); $P < 0.001$]. Empirical therapy was deemed to be adequate in 51 of the 64 patients (80%). Inadequacy of empirical therapy was because of resistant organisms in 10 of 13 cases (77%) and sub-therapeutic dosing in 3 cases (23%). Factors analysed for association with receipt of adequate empirical therapy are listed in Table 1. Total LOS [median 55 days (IQR 36–79) versus 40 (IQR 20–70); $P = 0.08$], LOS before invasive candidiasis [median 15 days (IQR 7–27) versus 11 (IQR 3–24); $P = 0.15$] and LOS following invasive candidiasis [median 34 days (IQR 13–62) versus 21 (IQR 9–44); $P = 0.11$] did not differ significantly in those treated with adequate empirical therapy relative to the entire study cohort. Patients treated with adequate empirical therapy were more likely to have had infection with a *C. albicans* isolate [28/51 (55%) versus 2/13 (15%); RR 3.57 (CI 0.98–13.08); $P = 0.01$], received initial therapy with a drug other than fluconazole [29/51 (57%) versus 1/13 (8%); RR 7.39 (CI 1.10–49.33); $P = 0.002$] and had a shorter in-hospital treatment course [median 21.6 days (IQR 12.3–34.2) versus 52.8 (IQR 16.7–55.4); $P = 0.05$] relative to those treated inadequately with empirical therapy.

Mortality and risk factors for death

All-cause in-hospital mortality was 82/199 (41%). In univariate analyses, increased mortality was associated with age ≥ 18, underlying heart disease, renal failure and requirement for ICU support as shown in Table 2. No clear relationship between the time from culture draw to first adequate therapy and death was observed; the in-hospital mortality rates were 8/32 (25%) when patients received an effective antifungal within 1 day of culture draw, 16/33 (48%) between 1 and <2 days, 7/36 (19%) between 2 and <3 days, 6/17 (35%) between 3 and <4 days and 10/28 (36%) for 4 or more days after culture draw. There was a non-significant trend towards reduced mortality with any empirical therapy (regardless of adequacy) [21/64 (33%) versus 61/135 (45%); RR 0.73 (CI 0.49–1.08); $P = 0.12$]. Empirical therapy with an adequate agent (isolate susceptible *in vitro*) was associated with a significant reduction in all-cause mortality [14/51 (27%) versus 68/148 (46%); RR 0.60 (CI 0.37–0.96); $P = 0.02$]. In the absence of any antifungal therapies in-hospital mortality was increased [24/34 (71%) versus 58/165 (35%); RR 2.01 (CI 1.49–2.71), $P < 0.001$]. Multivariate logistic regression techniques were used to assess risk factors for death in patients with invasive candidiasis, and the final model ($n = 199$) included increasing age, requirement for ICU support and receipt of adequate empirical therapy as shown in Table 3.

Discussion

Candida spp. infections are the most common invasive fungal infection and account for 8% of all nosocomial bloodstream infections.[1] With an attributable mortality rate of 40–49%, invasive candidiasis is gaining increased attention, as there remains tremendous potential to reduce patient morbidity and mortality.[2–5] While newer therapeutic options are available, they are associated with significant cost relative to traditional therapies such as fluconazole and amphotericin B deoxycholate. Early empirical therapy is purported to be critically important in patients at risk of invasive candidiasis. However, this remains an uncommon practice. In a recent study by Morrell *et al.*[19] that assessed the impact of time to treatment on patient outcome, only 15% of patients were receiving antifungal therapies at the time of positive cultures being identified.

The primary objective of this study was to evaluate the effect of adequate empirical antifungal therapy on the outcome of patients with invasive candidiasis. Empirical therapy was only used in one-third of patients with documented invasive candidiasis. Encouragingly, those at highest risk of invasive candidiasis because of immune-suppression on the basis of transplant status or treatment for active malignancy were more likely to receive empirical therapy. When empirical therapy was identified to be adequate, this resulted in improved patient survival. A paradoxical increase in treatment duration and trend towards prolonged hospital stay among those patients treated with adequate empirical therapy as compared with inadequate or no empirical therapy may be explained in part by the fact that those patients who had a greater illness burden were more likely to receive empirical therapy.

Table 1. Univariate analysis of factors associated with adequate empirical therapy in patients with invasive *Candida* spp. infection

Factor	Adequate therapy rate		RR (95% CI)[a]	*P* value
	with factor	without factor		
Heart disease	17/59 (29)	34/140 (24)	1.19 (0.72–1.95)	0.59
CVA	1/6 (17)	50/193 (26)	0.64 (0.11–3.91)	1.00
COPD	0/16 (0)	51/183 (28)	–	0.01
DM	10/36 (28)	41/163 (25)	1.10 (0.61–1.99)	0.83
Premature	4/11 (36)	47/188 (25)	1.45 (0.64–3.30)	0.48
RA	0/4 (0)	51/195 (26)	–	0.57
Renal failure	4/26 (15)	47/173 (27)	0.57 (0.22–1.44)	0.24
IHD	2/10 (20)	49/189 (26)	0.77 (0.22–2.73)	1.00
Malignancy	23/66 (35)	28/133 (21)	1.65 (1.04–2.64)	0.04
leukaemia	11/21 (52)	40/178 (22)	2.33 (1.43–3.81)	0.006
lymphoma	1/5 (20)	50/194 (26)	0.78 (0.13–4.55)	1.00
MM	1/3 (33)	50/196 (26)	1.31 (0.26–6.60)	1.00
solid organ	10/37 (27)	41/162 (25)	1.07 (0.59–1.93)	0.84
Transplant recipient	6/13 (46)	45/186 (24)	1.91 (1.01–3.62)	0.10
SCT	3/5 (60)	48/194 (25)	2.43 (1.14–5.17)	0.11
solid organ	3/8 (38)	48/191 (25)	1.49 (0.59–3.77)	0.42
ICU	26/102 (25)	25/97 (26)	0.99 (0.62–1.59)	1.00
Male sex	28/103 (27)	23/96 (24)	1.13 (0.70–1.83)	0.63
Age <18	12/29 (41)	39/170 (23)	1.80 (1.08–3.01)	0.06
Community onset	5/34 (15)	46/165 (28)	0.53 (0.23–1.23)	0.13
Prophylaxis	9/10 (90)	42/189 (22)	4.05 (2.89–5.68)	<0.001

CVA, cerebral vascular accident; COPD, chronic obstructive lung disease; DM, diabetes mellitus; RA, rheumatoid arthritis; IHD, intermittent haemodialysis; MM, multiple myeloma; SCT, stem cell transplant.

[a]RR is the proportion of patients that received adequate empirical treatment with a factor as opposed to those without the factor under evaluation. A RR of >1 would indicate that a factor is associated more frequently with adequate empirical therapy.

Inappropriate initial antimicrobial therapies have been linked with increased patient fatality.[14–17,24,25] Subsequent corrected regimens following microbiological identification of the pathogen have not been associated with improved patient survival, thus highlighting the critical importance of correct initial antimicrobial management.[26,27] Unfortunately, *Candida* spp. bloodstream infections have among the highest rates of inappropriate empirical therapies.[17] Patient factors associated with inadequate empirical therapy have received limited attention. In this study, patient demographic factors were not predictive of individuals at risk of inappropriate empirical therapy. Only patients with a history of chronic obstructive lung disease were identified as being less likely to receive appropriate therapy and this may have been influenced by the small sample size. Interestingly, there was a strong but non-significant trend towards children being more likely to receive adequate empirical therapy.

Few studies have specifically addressed the role of timing of antifungal therapies and patient outcomes in invasive candidiasis. Morrell *et al.*[19] identified that any delay in administration of antifungal therapy >12 h following blood culture draw was associated with an increased risk of mortality (RR 2.1). Garey *et al.*[18] further demonstrated in a multicentre retrospective study that for each successive day of delay in receipt of fluconazole treatment there was an increase in patient mortality. Lastly, Kumar *et al.*[28] were able to demonstrate an increase in mortality with each hour of treatment delay in fungal septic shock (RR 1.06). These studies, while provoking, are limited in that none consistently incorporated antifungal susceptibility testing into determination of appropriateness of therapy, and either did not describe treatment regimens or focused solely on fluconazole. While we found that adequate empirical therapy was associated with an improved outcome, we did not find a progressively increased risk for death associated with a daily delay in institution of adequate therapy.

One of the most commonly cited reasons for inadequate empirical antifungal therapies is the inability to clinically distinguish invasive candidiasis from other infections. Most authors recommend profiling patients to identify clinical risk factors associated with increased risk of invasive candidiasis and to use these to target patients most likely to benefit from empirical therapy. However, decisions based on clinical grounds alone are problematic as many of the cited risk factors for invasive candidiasis are those shared by opportunistic bacterial pathogens. While decision analysis algorithms exist, their application remains limited.[29] Certainly rapid, non-culture-based techniques of identifying invasive candidiasis would enable prompt treatment of those at risk thereby minimizing unnecessary antifungal exposures that may result in increased cost, drug toxicities and emergence of resistance.[30–32]

The strengths of this study consist of the inclusion of all documented cases of invasive candidiasis occurring over a 5 year time period identified via a regional centralized microbiology laboratory servicing all acute care hospitals and community collection sites. The patient population is heterogeneous, and detailed information was available with respect to

Table 2. Univariate analysis of factors associated with death in patients with invasive *Candida* spp. infection

Factor	Fatality rate		RR (95% CI)[a]	*P* value
	with factor	without factor		
Heart disease	32/59 (54)	50/140 (36)	1.52 (1.10–2.10)	0.02
CVA	4/6 (67)	78/193 (40)	1.65 (0.91–2.98)	0.23
COPD	7/16 (44)	75/183 (41)	1.07 (0.60–1.91)	1.00
DM	13/36 (36)	69/163 (42)	0.85 (0.53–1.36)	0.58
Premature	3/11 (27)	79/188 (42)	0.65 (0.24–1.73)	0.53
RA	1/4 (25)	81/195 (42)	0.60 (0.11–3.31)	0.64
Renal failure	16/26 (62)	66/173 (38)	1.61 (1.12–2.31)	0.03
IHD	5/10 (50)	77/189 (41)	1.23 (0.64–2.33)	0.74
Malignancy	27/66 (41)	55/133 (41)	0.99 (0.69–1.41)	1.00
leukemia	9/21 (43)	73/178 (41)	1.05 (0.62–1.77)	1.00
lymphoma	3/5 (60)	79/194 (41)	1.47 (0.71–3.07)	0.40
MM	2/3 (66)	79/196 (40)	1.65 (0.73–3.74)	0.57
solid organ	13/37 (35)	69/162 (43)	0.82 (0.51–1.33)	0.46
Transplant recipient	5/13 (38)	77/186 (41)	0.93 (0.46–1.89)	1.00
SCT	1/5 (20)	81/194 (42)	0.48 (0.08–2.79)	0.65
solid organ	4/8 (50)	78/191 (41)	1.22 (0.60–2.50)	0.72
ICU	52/102 (51)	30/97 (31)	1.65 (1.16–2.35)	0.006
Male sex	42/103 (41)	40/96 (42)	0.98 (0.70–1.36)	1.000
Age <18	5/29 (17)	77/170 (45)	0.38 (0.17–0.86)	0.004
Community onset	12/34 (35)	70/165 (42)	0.83 (0.51–1.36)	0.57
Prophylaxis	3/10 (30)	79/189 (42)	0.72 (0.27–1.88)	0.53
C. albicans versus other	37/103 (36)	45/96 (47)	0.77 (0.55–1.07)	0.15
Empirical therapy	21/64 (33)	61/135 (45)	0.73 (0.49–1.08)	0.12
Adequate empirical therapy	14/51 (27)	68/148 (46)	0.60 (0.37–0.96)	0.02
Adequate first drug	35/121 (29)	47/78 (60)	0.48 (0.34–0.67)	<0.001
Adequate overall	47/146 (32)	35/53 (66)	0.49 (0.36–0.66)	<0.001
No drug	24/34 (71)	58/165 (35)	2.01 (1.49–2.71)	<0.001
Initial therapy with fluconazole versus other drug	33/108 (31)	25/57 (44)	0.70 (0.46–1.06)	0.12

CVA, cerebral vascular accident; COPD, chronic obstructive lung disease; DM, diabetes mellitus; RA, rheumatoid arthritis; IHD, intermittent haemodialysis; MM, multiple myeloma; SCT, stem cell transplant.
[a]RR is the proportion of patients that died with a factor as opposed to those without the factor under evaluation. A RR of >1 would indicate that the factor is associated more frequently with death.

demographics, co-morbidities, treatment modalities and time to treatment. Furthermore, antifungal susceptibility testing was performed on 89% of clinical samples providing assurance of *in vitro* efficacy rather then relying on predicted susceptibility profiles. This study is limited by the lack of inclusion of an objective assessment of illness burden such as APACHE II scoring. Furthermore, transient patient factors occurring during the episode of invasive candidiasis such as acute renal failure, requirement for mechanical ventilation, central venous catheterization, receipt of total parenteral nutrition (TPN) and neutropenia were not available using the combined databases.

Table 3. Logistic-regression modelling of risk factors for mortality in patients with invasive *Candida* spp. infection

Variable	OR (95% CI)	*P* value
Age 18–64[a]	4.07 (1.32–12.52)	0.01
Age 65–79[a]	9.00 (2.76–29.37)	<0.001
Age ≥80[a]	20.98 (5.26–83.73)	<0.001
ICU admission	3.79 (1.93–7.44)	<0.001
Adequate empirical therapy	0.46 (0.22–1.00)	0.05

The final model ($n = 199$) had good calibration (goodness of fit $P = 0.32$) and discrimination (area under ROC curve = 0.75).
[a]As compared with reference category age <18 years.

Our study demonstrates that empirical antifungal therapy, even in those patients at high risk, remains an uncommon practice. Appropriate empirical antifungal therapy, while seldom applied, is associated with an increased rate of patient survival. Future research is needed to more accurately define patients who will benefit from early empirical antifungal therapy while awaiting culture confirmation.

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Transparency declarations

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