Is Timely and Appropriate Antifungal Drug Enough for Survival of Adult Cases with Candidaemia? Five-year Experience

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ABSTRACT

Objective: *Candidaemia is the fourth most common cause of nosocomial bloodstream infections. The objective of this paper was to evaluate the risk factors associated with mortality in patients with candidaemia with respect to Candida species and their susceptibilities, retrospectively.*

Methods: *All consecutive patients who developed candidaemia at an 800-bed training and research hospital were enrolled in this retrospective, observational, single centre study during the period June 2006 to December 2011.*

Results: *A total of 97 candidaemia episodes were identified in 97 patients during the study period with an overall incidence of four episodes/10 000 admissions in adults. Crude 30-day mortality rates among patients with candidaemia were 56% (55 of 97 cases). Urinary catheterization, immunosuppressive therapy, acute physiology and chronic health evaluation (APACHE) II score (≥ 16) and hypoalbuminaemia were found to be independent risk factors for fatal candidaemia.*

Conclusions: *Adult cases with candidaemia who have risk factors associated with mortality are more likely to have poor prognosis despite appropriate and timely initiated antifungal drug treatment. Empiric antifungal drug should be tailored according to the severity of the patients' conditions and local antifungal susceptibility.*

Keywords: Adult, antifungal drug, candidaemia, mortality, risk factors

¿Es el Uso Oportuno y Adecuado de Antimicóticos Suficiente para la Supervivencia de Casos de Adultos con Candidemia? Cinco Años de Experiencia

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RESUMEN

Objetivo: *La candidemia es la cuarta causa más común de infecciones nosocomiales del flujo sanguíneo. El objetivo del presente trabajo fue evaluar los factores de riesgo asociados con la mortalidad en pacientes con candidemia con respecto a las especies de Candida y sus susceptibilidades, de manera retrospectiva.*

Métodos: *Todos los pacientes consecutivos que desarrollaron candidemia en un hospital de capacitación e investigación de 800 camas, fueron inscritos en este estudio retrospectivo, observacional, monocéntrico, durante el período de junio de 2006 a diciembre de 2011.*

Resultados: *Se identificaron un total de 97 episodios de candidemia en 97 pacientes durante el período de estudio con una incidencia general de cuatro episodios/10 000 ingresos en adultos. Las tasas brutas de mortalidad de 30 días entre los pacientes con candidemia fueron 56% (55 de 97 casos). Se halló que la cateterización urinaria, la terapia inmunosupresiva, y la puntuación (≥ 16) de la escala de Evaluación de la fisiología aguda y salud crónica (APACHE II) así como la hipoalbuminemia, constituyen factores de riesgo para una candidemia fatal.*

Conclusiones: *Los casos adultos con candidemia que tienen factores de riesgo asociados con mortalidad son más propensos a tener un pronóstico pobre a pesar del tratamiento apropiado y*

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oportuno con medicamentos antimicóticos. Los antimicóticos empírico se deben adaptar según la severidad de las condiciones de los pacientes y la susceptibilidad antifúngica local.

Palabras claves: Adulto, antimicóticos, candidemia, mortalidad, factores de riesgo

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INTRODUCTION

Candida genus is a member of normal flora in the gastrointestinal tract and adult skin and the yeasts which contain approximately 200 species that are widespread in nature (1). Candidaemia is defined as growth of a Candida species in at least one blood culture with clinical findings (2). Candidaemia is the fourth most common cause of nosocomial bloodstream infections and comprise nine per cent of the cases in a national survey of hospitals in the United States of America (USA) from 1995 to 2002 (3, 4). The incidence of nosocomial candidaemia varies by intensive care unit (ICU), ward, hospital and countries. Costs increase $40 000 per episode of candidaemia (5, 6). Candida species, which cause candidaemia, vary in the studies; for instance, 46% of 2019 bloodstream isolates were reported as *C albicans* in a multicentre surveillance between 2004 and 2008 in the USA (7). *C glabrata* was reported to be responsible for 26% of all candidaemia cases, followed by *C parapsilosis* (16%), *C tropicalis* (8%) and *C krusei* [3%] (7−9). Identification and susceptibility of isolated Candida species are crucial to initiate the appropriate antifungal drug that affects the prognosis, due to increasing primary and acquired resistance among Candida species (2, 10). Requirement of standardized antifungal susceptibility tests is clear, since timely and appropriate antifungal treatment and low fluconazole resistance rates were reported to be related to lower mortality rates (11, 12).

The aim of this study is to evaluate the risk factors associated with mortality in patients with candidaemia with respect to Candida species and their susceptibilities, retrospectively.

SUBJECTS AND METHODS

Study design and data collection

All consecutive patients who developed candidaemia at a training and research hospital that includes three ICUs (resuscitation, surgery, neurosurgery) and 800 beds with about 42 000 admissions per year were enrolled in the study during the period June 2006 to December 2011. This study was approved by the institutional review ethics committee. In this retrospective observational study, the patients who had systemic inflammatory response (fever, hypothermia, leukocytosis or leukopenia, tachycardia, tachypnoea, hypotension) with at least one blood culture that yielded any Candida species were included in the study. Patients who had insufficient information or contamination regarding blood culture that yielded any Candida species were excluded from this study. The following data were extracted from the patient charts: age, gender, co-morbidities and risk factors in the preceding 30 days before the onset of candidaemia (recent surgery, central venous access devices (CVADs), neutropaenia, hyperalimentation, and administration of corticosteroids and antimicrobials or systemic antifungal agents. Acute physiology and chronic health evaluation (APACHE) II scores, laboratory findings, clinical signs of sepsis, results of diagnostic studies, antifungal treatment and outcome were collected. The number of admissions to hospital in a year was acquired from the hospital administration. Empiric antifungal drug was initiated if a patient had persistent fever with risk factors for fungal infection and was under antibiotic treatment or if a blood culture of a patient who had clinical signs and symptoms in accordance with infection yielded yeasts, pending identification and susceptibility testing. Antifungal drug was changed depending on identified Candida species and antifungal susceptibility.

Definitions

Adults who were older than 14 years old were included in the study. Relapse was defined as yielding a positive blood culture within 30 days of the first positive blood culture after clinical and microbiological response. Central-line associated candidaemia was defined as peripheral blood culture taken at least two hours before catheter culture that yielded the same Candida species which grew up in catheter culture or removed catheter tip culture (≥ 15 CFU on the plates which tip was rolled on it). Neutropaenia was defined as an absolute neutrophil count (ANC) of $< 1.0\times10^9$/L and impaired renal function was a serum creatinine > 0.17 mmol/L. Sepsis and severe sepsis were defined according to international definitions (13). Immunosuppressive therapy was defined as cytotoxic therapy or total body irradiation within three months before the onset of candidaemia or systemic cortisone (≥ 40 mg per day at the start of cortisone treatment) within one month before the onset of candidaemia. The antifungal drug was initiated on the day of or after the date when the blood culture that yielded positive for any Candida species was drawn. Overall mortality was defined as all death within 30 days after diagnosis. If C-reactive protein (CRP) was 8 mg/dL or more, it was considered as elevated. If aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 40 IU/L and more, they were considered as elevated. Hypoxia was defined as oxygen saturation less than 90% or arterial oxygen pressure less than 60 mmHg. Diarrhoea was defined as three or more watery

stools in a day. Anaemia was defined as haemoglobin levels below 13 g/dL in men and below 12 g/dL in women by World Health Organization criteria. Thrombocytopaenia was defined as a platelet count ≤ 150 x 10^9 L. Leukocytosis was defined as any value above 10 x 10^9 L. Leukopenia was defined as any value under 4 x 10^9 L. Hypoalbuminaemia was defined as a serum albumin level less than 3.5 g/dL. The incidence of candidaemia was calculated as the ratio of the total number of patients per 10 000 admissions.

Microbiological methods

In total, 16 943 blood samples inoculated aseptically into bottles of the BacT/Alert 3D automated colorimetric system (bioMerieux, Marcy l'Etoile, France) were incubated for seven days within the study time. Isolated yeasts from blood cultures were identified by morphologic examination on Sabouraud Dextrose Agar (Oxoid, Istanbul, Turkey) plate, germ-tube formation and API ID 32C (bioMerieux, France) at the species level. ATB Fungus 2 microdilution kit was used (biomerieux, Lyon, France) for susceptibility testing according to the CLSI (formerly NCCLS) broth microdilution M27-A2 protocol as follows: for amphotericin B, 5-flucytocine, fluconazole, itraconazole and voriconazole (14). Resistance was defined as minimum inhibitory concentration (MIC) ≥ 64 mg/L (and susceptible dose-dependent (S-DD) as an MIC of 16–32 mg/L) for fluconazole, MIC ≥ 1 mg/L for itraconazole and MIC ≥ 4 mg/L for voriconazole, MIC > 0.5 mg/L for amphotericin B and MIC > 0.5 mg/L for flucytosine. *C parapsilosis* ATCC 22019 and *C krusei* ATCC 6258 were used as quality control strains. Repetitive strains, which were isolated from the same materials of the same patients, and isolates which were unidentified at the species level, were excluded. *C krusei* was defined as resistant to fluconazole due to intrinsic resistance.

Statistical analysis

Data were analysed using SPSS 13.0 (Chicago, IL, USA). Continuous variables were described as mean ± standard deviation and range. Percentile values were described without decimal. To evaluate factors associated with mortality, univariate analyses were performed using the Pearson χ^2 test, or Fisher's exact test for categorical variables and unpaired Student's *t*-test for continuous variables. Bivariate logistic regression analysis was conducted to obtain unadjusted odds ratios and revealed as (odds ratio (OR), 95% confidence interval, *p*-value) candidaemia in comparison of both survivor and non-survivor groups. Risk factors that reached statistical significance ($p < 0.05$) using a forward selection process remained in the model. All tests were based on two-tailed tests and *p*-values < 0.05 were considered as significant.

RESULTS

A total of 97 candidaemia episodes were identified in 97 patients with an overall incidence of 4.19 episodes/10 000 admissions in adults during the study period. From 2006 to 2011, incident density rates were calculated as 2.38 (n = 5), 3.57 (n = 15), 5 (n = 21), 5.47 (n = 23), 4.04 (n = 17) and 3.8 (n = 16) per 10 000 admissions in each year, respectively. Of 97 patients, 51 cases were male, mean age was 50.51 ± 21.12 years, range of ages was between 15 and 90 years. Candida isolates of ICU patients composed 76% (n = 74/97) of all isolates (*C parapsilosis* (n = 24/39, 63%), *C albicans* (n = 21/32, 21%) and *C tropicalis* (n = 13/19, 68%) and others) followed by the haematology ward (n = 12, 12%) and surgery ward (n = 9, 9%). Underlying conditions were recorded in 62 (63%) patients, and surgery was the most common co-morbid factor, as recorded in 55 cases (56%). Mean APACHE II scores of the patients (n = 74) were 12.73 ± 6.24. Central-line catheter (n = 82, 84%) and urinary catheter (n = 81, 83%) were the most common risk factors in the cases. Hypoxia (n = 49) and sepsis (n = 36) were the most common clinical findings in the cases. C-reactive protein (CRP) elevation (n = 94) and hypoalbuminaemia (n = 90) were the most common laboratory findings in the patients (Tables 2, 3). Concurrent bacteraemia developed with methicillin resistant *S aureus* (MRSA) in 11 cases and methicillin resistant coagulase negative staphylococci (MR-CNS) in 10 cases, *P aeruginosa* in three cases, *E* coli in two cases, and *A baumannii*, and *S marcescens* in one case each. Candida strains were also isolated from urine cultures (n = 27), and catheter cultures (n = 9). Central-line associated candidaemia developed with *C parapsilosis* in five cases and *C albicans* in four cases. Peritoneal fluid cultures yielded *C albicans* in three cases, *C parapsilosis* in two cases and *C tropicalis* in one case (Table 1). Fluconazole was initiated as empirical antifungal drug in 20 (62%) cases with *C albicans*, 26 (68%) cases with *C parapsilosis* and eight cases (42%) with *C*

Table 1: Candida species and their antifungal susceptibilities of the patients with candidaemia (n = 97)

Antifungal drugs	FCZ			ICZ			VCZ			5-FC			AmB		
Species (n, %)	S n (%)	I n (%)	R n (%)	S n (%)	I n (%)	R n (%)	S n (%)	I n (%)	R n (%)	S n (%)	I n (%)	R n (%)	S n (%)	I n (%)	R n (%)
C parapsilosis (38, 39)	32 (85)	2 (5)	4 (10)	34 (90)	2 (5)	2 (5)	33 (86)	2 (6)	3 (8)	38 (100)	0 (0)	0 (0)	38 (100)	0 (0)	0 (0)
C albicans (32, 32)	25 (78)	1 (6)	6 (16)	27 (84)	2 (6)	3 (10)	30 (90)	0 (0)	2 (10)	32 (100)	0 (0)	0 (0)	32 (100)	0 (0)	0 (0)
C tropicalis (19, 19)	7 (37)	0 (0)	12 (63)	10 (53)	4 (21)	5 (26)	16 (84)	0 (0)	3 (16)	19 (100)	0 (0)	0 (0)	17 (89)	0 (0)	2 (10)
C glabrata (5,5)	2 (40)	2 (40	1 (20)	3 (60)	1 (20)	1 (20)	4 (80)	0 (0)	1 (20)	5 (100)	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)
C krusei (2, 2)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)	1 (50)	0 (0)	1 (50)	1 (50)	1 (50)	0 (0)	2 (100)	0 (0)	0 (0)
C norvegensis (1, 1)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)

FCZ: fluconazole, ICZ: itraconazole, VCZ: voriconazole, 5-FC: 5-flucytosine, AmB: amphotericin B, S: susceptible, I: intermediate, R: resistant

tropicalis. Amphotericin B (AmB) was initiated as empirical antifungal drug in seven (21%) cases with *C albicans*, four (10%) cases with *C parapsilosis* and three cases (15%) with *C tropicalis*. Caspofungin (CAS) was initiated as empirical antifungal drug in five (15%) cases with *C albicans*, eight (21%) cases with *C parapsilosis*, and six cases (31%) with *C tropicalis.* Urinary catheterization (OR = 0.28; 95% CI: 0.08, 0.88; p = 0.03), immunosuppressive therapy (OR = 0.29; 95% CI: 0.09, 0.92; p = 0.039), APACHE II score (≥ 16) [OR = 0.3; 95% CI: 0.12, 0.75; p = 0.008] and hypoalbuminaemia

Table 2: Distribution of categorized variables by survival group in the patients with candidaemia (n = 97)

	Total (n, %)	Survivor (n = 42) n (%)	Non-survivor (n = 55) n (%)	Odds ratio (% 95 CI)	*p*
Age (years)	50.51 ± 21.124	49.13 ± 18.64	51.01 ± 19.43		0. 87
Male/female	49/48	22/20	27/28		0.748
Interventions					
Central venous catheter	(82, 84)	37 (88)	45 (81)		0.572
Urinary catheter	(81, 83)	31 (73)	50 (90)	**0.28 (0.08, 0.88)**	**0.03**
Total parenteral nutrition	(52, 53)	19 (45)	33 (60)		0.158
Surgery	(60, 61)	23 (54)	37 (71)		0.292
Transfusion	(53, 54)	23 (54)	30 (54)		0.983
Mechanic ventilation	(67, 69)	26 (61)	41 (74)		0.183
Broad-spectrum antibiotic use	(75, 77)	30 (71)	45 (81)		0.228
Underlying conditions					
Co-morbid conditions	(74, 76)	31 (73)	43 (78)		0.638
Immunosuppression therapy	(19, 19)	5(11)	14 (25)	**0.29 (0.09, 0.92)**	**0.039**
Neutropaenia	(18, 18)	10 (23)	8 (14)		0.247
Diabetes mellitus	(17, 17)	6 (14)	11 (20)		0.460
Malignancy	(31, 31)	17 (40)	14 (25)		0.117
Haematological disorders	(15, 15)	6 (14)	9 (16)		0.779
Respiratory tract diseases	(16, 16)	10 (23)	6 (10)		0.091
Clinical findings					
APACHE II score (≥ 16)	(35, 47)	9 (12)	26 (35)	**0.3 (0.12, 0.75)**	**0.008**
Gastrointestinal bleeding	(12, 12)	8 (19)	4 (7)		0.545
Hypoxia	(49, 50)	17 (40)	32 (58)		0.103
Septic shock (n = 16)	(16, 16)	6 (14)	10 (18)		0.607
Mucositis	(17, 17)	10 (23)	7 (12)		0.331
Diarrhoea	(12, 12)	8 (19)	4 (7)		0.119

APACHE = acute physiology and chronic health evaluation

Table 3: Laboratory and microbiological findings by survival group in the patients with candidaemia (n = 97)

	Total (n, %)	Survivor (n = 42) n (%)	Non-survivor (n = 55) n (%)	Odds ratio (%95 CI)	*p*
Laboratory findings					
CRP elevation	(83, 85)	38 (90)	45 (81)		0.26
Anaemia	(68, 70)	26 (61)	42 (76)		0.124
Hypoalbuminaemia	(65, 67)	21 (50)	44 (80)	**4 (1.63, 9.79)**	**0.002**
Decreased creatinine clearance	(18, 18)	7 (16)	11 (20)		0.675
Thrombocytopaenia	(27, 27)	13 (31)	14 (25)		0.55
ALT elevation	(25, 25)	11 (26)	14 (25)		0.935
AST elevation	(40, 41)	18 (42)	22 (40)		0.777
Microbiological findings					
Concurrent bacteraemia	(28, 28)	11 (26)	17 (30)		0.61
Candida growth in urine culture	(27, 27)	11 (26)	16 (29)		0.752
Candida growth in catheter culture	(9, 9)	3 (7)	6 (10)		0.728
Candida growth in peritoneal fluid	(6, 6)	3 (7)	3 (5)		0.733
Growth of *C albicans* species	(32, 32)	13 (31)	19 (34)		0.419
Growth of non-*C albicans* species	(65, 67)	31 (73)	34 (61)		0.21
Fluconazole resistance	(14, 14)	5 (11)	9 (16)		0.533
Fluconazole treatment	(50, 51)	20 (47)	30 (54)		0.499

CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CI: Confidence interval

(OR = 4; 95% CI: 1.63, 9.79; p = 0.002) were found to be independent risk factors for fatal candidaemia (Tables 2, 3). Crude 30-day mortality rates among patients with candidaemia were 56% (55 of 97 cases). Blood culture controls drawn 72 hours after antifungal treatment were negative in 45 patients of 55 fatal cases and all surviving patients. Caspofungin was initiated empirically in 18 of 42 survivor cases and 15 of 55 fatal cases (p = 0.109). Amphotericin B was initiated empirically in four of 42 survivor cases and 10 of 55 fatal cases (p = 0.26). Fluconazole was changed to CAS after 72 hours in nine survivor patients and nine non-survivor patients. Switching to either CAS or voriconazole did not achieve clinical response in two haematological patients who were under AmB or CAS treatment.

DISCUSSION

Candida bloodstream infections (CBI) are the fourth most common cause overall of haematogenous infections in the USA and they were reported as fourth to seventh in Europe (5, 15). Incidence of candidaemia in adult patients increased until 2009 and then decreased in each year at our hospital. The overall incidence of nosocomial candidaemia at our hospital – 4.19 cases per 10 000 hospital admissions – is higher than two of density figures which have been reported as 1.68, 5.6 and 0.58 per 10 000 hospital admissions in two university hospitals and one training and research hospital in Turkey, respectively (16−18). The incidence of bloodstream fungal infections was reported from 0.28 to 0.96 per 1000 admissions in the USA and from 0.2 to 0.38 in Europe, whereas these rates varied between 1.2 and 5.3 (0.2–0.5 cases per 1000 patient-days) in Latin America (5, 19, 20). Almost all studies from different countries and Turkey described increasing incidence density rates of CBIs with non-albican species as found in our study (17, 18, 21, 24). A few studies from Turkey, USA and Asia reported that non-albican species predominated among other species in candidaemia attacks as *C parapsilosis* predominated in our study, whereas other studies from Turkey and Europe revealed in favour of *C albicans* (8, 16, 17, 21, 24). Widespread azole use, fungal ecology of hospitals and countries cause diversity of species which cause candidaemia. *C parapsilosis* candidaemia was found to be related to vascular catheters and parenteral nutrition (25). *C tropicalis* was reported to be related to cancer and neutropaenia (28). *C krusei* and *C glabrata* fungaemias were reported to be associated with previous exposure to azoles (28). Most of these cases of candidaemia were from ICU and haematology wards as reported in other studies (29, 30). Patients who are followed-up at those wards are more likely to have candidaemia due to immune compression, broad spectrum antibiotic use, colonization of several body sites, disruption of physiological barriers in the digestive tract and other factors (29, 30). Colonization rates were reported between five and 15 per cent in patients who were admitted to ICU, but those rates progressively increase to 50−80% as a result of prolonged exposure to many risk factors, such as major surgery, parenteral nutrition, dialysis and antibiotics (31−33). However, only 5−30% of colonized patients will develop candidaemia, which is usually a late-onset ICU infection (34, 35). Wey and colleagues reported that patients receiving more than three antimicrobial drugs have 12.5 times higher risk for candidaemia (36). Central venous catheter, urinary catheter, co-morbid conditions, total parenteral nutrition, surgery, transfusion, mechanic ventilation and broad-spectrum antibiotic use were described to be risk factors that predisposed to candidaemia, as in our study (20, 22, 36).

Fluconazole sensitivity of *C parapsilosis* and *C albicans* isolates that comprised 73% of all Candida isolates indicates that fluconazole could be initiated for patients who have uncomplicated sepsis and normal renal and hepatic function and no history of azole exposure in ICU and other wards. Fluconazole resistance rates have been reported from 0.3 to 10% in different studies (37−41). But higher voriconazole resistance rates have been reported in *C tropicalis* isolates from patients with cancer or neutropaenia. Physicians should take into consideration development of candidaemia under voriconazole treatment due to increasing selection of voriconazole-resistant Candida species (26). Amphotericin B or ecinocandins should be chosen for patients who have history of azole exposure in case of development of *C krusei* and *C glabrata* fungaemias that have higher azole resistance rates, as in our study (42, 43). Itraconazole resistance rates in our study highlight azole resistance status in Turkey, as the study by Kiraz and Öz reported that only seven *C krusei* isolates were resistant to AmB, whereas 80% (n = 1653), 76% (n = 1572) and 99% (n = 2061) of all candida isolates were susceptible to fluconazole, itraconazole and amphotericin B, respectively (44).

As crude-30 day mortality rates were reported from 20% to 63%, rates of our study (56%) were similar to other studies from Turkey [56% and 58%] (16, 17, 20, 45). Delayed or inappropriate antifungal treatment decreases survival rates (12, 46, 47). Antifungal drug was initiated as soon as possible after identification of yeasts and their susceptibilities in our study. Attributed mortality was reported between 15% and 25% in adults (6, 7). Mean age (50 years) in our study was older than those reported in previous studies (48, 49). Urinary catheter, immunosuppression therapy, hypoalbuminaemia and APACHE II score (≥ 16) were determined to be risk factors associated with mortality in our study. Staying in ICU, mechanical ventilation, total parenteral nutrition, urinary catheterization, malignancy, any surgical procedures and central venous catheterization, no response to antifungal treatment, underlying disease other than trauma, high Charlson index, poor renal function and shock were described as mortality related risk factors in patients with candidaemia (17, 28, 50). Concurrent bacteraemia and fluconazole resistance were not determined to increase mortality rates in our study as the study of

Jutiamornlerd *et al* reported (50). Although previous studies recommended the removal of the catheter after identifying the candidaemia, Nucci and colleagues reported that catheter removal by 24 or 48 hours after treatment initiation had no effect on overall treatment response, mortality and mycological eradication in an analysis of 842 patients (6, 51, 52). Removing the catheter should be evaluated against the patient's benefits and harms. Severity of illness and underlying conditions of the patients are more likely to affect treatment response rates and prognosis. Ecinocandins, amphotericin B and voriconazole should be chosen if patients are haemodynamically unstable, or have CVADs, previous azole exposure or azole prophylaxis. Treatment should be continued at least two weeks following the last positive culture (6).

CONCLUSION

Adult cases with candidaemia and who have risk factors associated with mortality are more likely to have poor prognosis despite appropriate and timely initiated antifungal drug treatment. Empirical choice of antifungal drug should be tailored with respect to the severity of patients and local antifungal susceptibility.

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