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Effect of first-line antifungal treatment on ocular complication risk in *Candida* or yeast blood stream infection

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ABSTRACT

Objectives Ocular candidiasis (OC) can complicate *Candida* bloodstream infection (BSI). Antifungal treatment improves the prognosis of patients with BSI, but the effects of choice and timing of first-line medication on OC risk are incompletely understood. We explored the early treatments, risk factors and ocular presentations in *Candida* BSI.

Methods and analysis All patients (n=304) with *Candida* BSI during 2008–2017 at Oulu University Hospital were included. Those patients in whom clinical condition was appropriate for ocular examination (OE), including biomicroscopy (n=103), were carefully analysed by ophthalmologists. Criteria for patient selection were considered. *Candida* and yeast species, antifungal medications, echocardiography, underlying diseases and clinical properties of the patients with *Candida* BSI were analysed.

Results Clinical condition in 103 patients had been considered appropriate for OE. OC was diagnosed in 33 of the 103 patients. *Candida albicans* was the most common finding (88%) in OC. Patients in intensive care, alcohol-related conditions or poor prognosis were less frequently examined. Persistent candidemia increased the risk of OC. Chorioretinitis and endophthalmitis were diagnosed in 94% and 48% of the patients with OC, respectively. Any early antifungal treatment decreased the endophthalmitis risk. Echinocandin lowered the OC risk in those with central venous catheters (CVCs) or abdominal malignancy.

Conclusion Critical condition of patients with *Candida* BSI affects the selection and results of OE. OC was associated with *C. albicans* BSI especially among those with persistent candidemia, CVC or abdominal malignancy. Any early antifungal treatment reduced endophthalmitis risk. Early echinocandin treatment may reduce the risk of OC in selected patients.

Key messages

What is already known about this subject?

- *Candida* blood stream infection (BSI) may be complicated by ocular candidiasis (OC). *Candida albicans* is the most prevalent microbiological finding in OC.

What are the new findings?

- Our patient selection was carefully analysed and only those patients examined with biomicroscopy were included. Early antifungal treatment of *Candida* BSI reduced endophthalmitis risk. Early echinocandin treatment compared with fluconazole treatment reduced OC risk in patients with central venous catheter or abdominal malignancy.

How might these results change the focus of research or clinical practice?

- Early appropriate antifungal treatment can reduce risk of ocular complications in patients with *Candida* BSI. Early echinocandin treatment may reduce OC risk despite the low intraocular penetration.

INTRODUCTION

Candida bloodstream infection (BSI) is commonly associated with ocular complications. Routine ophthalmological examination (OE) has been recommended for all patients with *Candida* BSI by the Infectious Diseases Society of America,[1] although this practice remains controversial.[2–5] Different definitions of probable or proven ocular candidiasis (OC) have led to variations in the conclusions of rate and outcomes of OC.[3 6] Critical condition of patients with *Candida* BSI may not warrant OE and all published data on OC are based on selected patient material.[6]

Candida BSI associates with serious underlying medical conditions and high mortality.[1] Critically ill patients in intensive care units, those with major abdominal surgical procedures and patients with neutropenia are at highest risk. The patients frequently suffer from *Candida* colonisation of indwelling catheters, translocation from the gut to the bloodstream or anastomotic leakage after laparotomy. *Candida* endocarditis, that is, infectious process of heart, is a rare and serious complication with a high potential of affecting peripheral organs. *C albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* or *C. krusei* are the most common isolates in blood cultures although other *Candida* spp can be found.[7] *C. albicans* is the most common finding in OC.[2–5]

Echinocandins with broad-spectrum activity against *Candida* spp are commonly recommended for *Candida* BSI treatment. This group of antifungals diffuses poorly into the vitreous humour.[1 8] Fluconazole, an agent active mainly against *C. albicans*, is more efficient in ocular penetration following systemic administration. Early appropriate antifungal treatment should reduce the risk of systemic and local complications in *Candida* BSI.[1] However, the effects of early antifungal treatment decisions on presentation of OC are incompletely understood.[6]

In our study, we carefully defined the properties of patients with *Candida* BSI who were examined or not examined by ophthalmologists due to their critical clinical condition. We investigated the role of choice and timing of early antifungal treatments on the risk of OC. We also explored various clinical features of the patients with OC in the cohort of patients with *Candida* BSI treated during 2008–2017. Finally, we aimed to identify risk profiles associated with OC and explored the detailed ocular findings of OC among our patient population.

MATERIALS AND METHODS

Setting, patients and study design

All patients (n=304) with *Candida* BSI during 2008–2017 treated at Oulu University Hospital responsible for tertiary care for a population of approximately 400 000 inhabitants were included. Thirty-three of these patients were transferred into other hospitals for treatment or follow-up and were thus excluded from the analysis involving the OEs; the remaining 271 *Candida* BSI cases were evaluated. Candidemia was defined as the presence of at least one blood culture positive for *Candida* sp.[1 9] *Candida*-positive blood culture at least 72 hours after active antifungal treatment (n=81) was considered persistent (median 5 days). If a patient had more than one candidemia episode, only the first episode was analysed. The study followed the tenets of the Declaration of Helsinki.

Blood cultures and microbiological analysis

Microbiological laboratory data were collected from the laboratory records. Blood culture samples were collected from the study subjects based on clinical judgement whenever BSI was suspected. Blood cultures were carried out by an automated continuous monitoring screening system of BacT/Alert and identified to species level (bio Mérieux, Marcy-l'Etoile, France). In vitro antifungal susceptibility to fluconazole, voriconazole, echinocandins and amphotericin B was determined with minimum inhibitory concentration gradient strip method (E-test) according to manufacturer's guidelines. Decision on number of blood cultures was based on clinical consideration (range 2–10, median 4).

Candida BSI treatment guidelines

In patients without neutropenia, Oulu University Hospital guidelines recommended during the study years administration of either empirical intravenous fluconazole (800 mg starting dose, followed by 400 mg daily) or intravenous echinocandin (caspofungin or micafungin according to generally accepted dosing) whenever *Candida* BSI is suspected. In patients with neutropenia with suspicion of candidemia, echinocandin was recommended. For the study period, caspofungin (70 mg starting dose, followed by 50 mg (<80 kg) or 70 mg (>80 kg) daily) has been used. Delay of at least 12 hours from the time when the first positive blood culture was drawn was recorded. Prompt removal of central venous catheters (CVCs) was recommended. The hospital guidelines recommend all patients to be considered for echocardiography (transthoracic: 185 patients, transoesophageal: 24 patients) to search for endocarditis. All patients with *Candida* BSI were recommended to be considered for a possibility of intraocular candidemia complications.

Ophthalmological evaluation and definitions

Comprehensive OE included measurements of visual acuity, intraocular pressure and biomicroscopy evaluations. Best corrected visual acuity measurements were converted to a logarithm of the minimum angle of resolution (logMAR) for analysis. Some of the patients were evaluated during the consultation visit in the intensive care unit only by direct and/or indirect ophthalmoscopy and those most severely ill could not be examined due to lack of cooperation. The ocular complications of *Candida* BSI documented included endophthalmitis defined as vitritis or fluffy lesions extending into the vitreous body and/or chorioretinitis including focal white infiltrates restricted to the chorioretinal layers either in macular area or peripheral retina. Also, data from haemorrhages in optic disc or retina as well as macular oedema were collected.

Clinical data collection and statistical analysis

Data of patient history, previous diagnoses, foreign materials, CVCs or other foreign materials, deep infection foci and antifungal treatments were collected. The IBM SPSS Statistics V.27 was used for statistical analysis and the p value of <0.05 was considered as statistically significant. The X^2 test was used for identifying differences between categorical variables. T-test was used for finding the differences in continuous variables between two groups.

RESULTS

Patient selection and microbiological finding

Table 1 summarises the study population (n=304) divided according to the causative *Candida* spp. The most common blood culture findings were *C. albicans* (63%, n=192), *C. glabrata* (18%, n=54) and *C. parapsilosis* (7%, n=20). In addition, 38 cases of other species were identified (*C. krusei* (n=7), *C. lusitaniae* (n=5), *C. guilliermondii* (n=1), *C. tropicalis* (n=6), *C. kefyr* (n=1), *C. inconspicua* (n=2), and other yeasts including *Saccharomyces cerevisae* (n=11), *Geotrichum* (n=2), and *Rhodotorula* (n=3)). There

Table 1 *Candida* isolates in blood cultures

	C. albicans	*C. glabrata*	*C. parapsilosis*	Other
Total, n (%)	192 (63)	54 (18)	20 (7)	38 (13)
Male	101 (53)	29 (54)	13 (65)	20 (53)
Female	91 (47)	25 (46)	7 (35)	18 (47)
Mean age ±SD (years)	61±18*	65±15	66±13	59±17
Ocular examination	73 (38)	16 (30)	6 (30)	8 (21)
Intensive care unit	42 (22)	7 (13)	4 (20)	7 (18)
Abdominal malignancy	48 (23)	15 (28)	2 (10)	4 (11)
Leukaemia or lymphoma	16 (8)	0 (0)	2 (10)	4 (11)
Abdominal complication	42 (22)	21 (39)	4 (20)	10 (27)
Neurological or psychiatric	35 (18)	10 (19)	3 (15)	9 (24)
Injury	8 (4)	1 (2)	2 (10)	0 (0)
Alcohol abuse	15 (8)	7 (13)	2 (10)	7 (18)
Intravenous drug abuse	8 (4)	0 (0)	1 (5)	5 (13)
Central venous catheter	98 (51)	26 (48)	6 (30)	16 (42)
Autoimmune disease	9 (5)	0 (0)	2 (10)	2 (5)
Endovascular or valve prosthesis	7 (4)	1 (2)	0 (0)	1 (3)
Endocarditis	6 (3)	0 (0)	2 (10)	2 (5)
No foreign body	59 (31)	15 (28)	7 (35)	17 (45)

The three most common species of *Candida* (*C. albicans, C. glabrata, C. parapsilosis*) and all other species (other) are shown. Gender and age distribution and number of patients examined by an ophthalmologist according to microbiology are presented. The underlying conditions and properties of the patients associated with the development of candidemia are also included.
*The patients with *C. albicans* were younger than those with *C. glabrata or C. parapsilosis* (p<0.05).

were no statistically significant differences in the patient characteristics or known risk factors for candidemia between the different *Candida* spp. Abdominal complications or abdominal malignancies were the most common predisposing conditions associated with the *Candida* BSI. About half (n=146) of the patients had CVCs.

Clinical features of patients examined by an ophthalmologist

Table 2 summarises the properties of patients who were carefully examined by an experienced ophthalmologist including, for example, comprehensive OE by biomicroscopy (n=103). The table also shows properties of patients (n=155) not examined by an ophthalmologist. Thirty-three patients were excluded due to their transfer to other hospitals. Patients evaluated by direct and/or indirect ophthalmoscopy (n=13, 5%) only were also excluded. The examined patients were younger (57 vs 63, p<0.01) than those who were not examined. Patients who were treated at intensive care units (p<0.05) or had alcohol abuse (p<0.01) were less often evaluated. Especially those who died within 3 months from the positive blood culture were rarely examined by ophthalmologists (p<0.001). The median time from positive blood culture to OE was 5.5 days (range 1–32 days).

Clinical features of patients with OC

Comprehensive OE was performed in 103 of the 271 (34%) patients summarised in table 3. Thirty-five patients examined had previously been diagnosed with another eye disease such as cataract, age-related macular degeneration, open-angle glaucoma or vitreous detachment. Findings consistent with OC criteria were found in 33 of the 103 patients (32%). Forty-six per cent of the patients with OC were men and the average age of all patients with OC was 55 years. Those below 40 years of age were less frequently affected by OC when compared with patients older than 40 years (p<0.05). *C. albicans* was the most common causative species in 88% of all OC cases. The features of OC caused by *C. albicans* or non-*albicans* are presented in table 4. Chorioretinitis was found in 94%, endophthalmitis in 48% and both in 42% of the OC cases. A majority of the patients, 94%, had bilateral involvement of OC. Macular lesion was noted in 67%, macular oedema in 9%, retinal haemorrhages in 36% and haemorrhages in optic disc in 9% of the patients with OC. Bleeding in retina and/or optic disc and endophthalmitis were mostly found in patients with *C. albicans* infection compared with OC due to other *Candida* spp. Vitrectomy was performed to two patients only, and three patients underwent vitreous aspiration. Intraocular pressure was at similar level in the primary and at the follow-up examinations (from 10.3±3.9 to 11.1±4.2 mm Hg (p=0.310) and from 10.7±4.1 to 11.4±3.7 mm Hg (p=0.463) in right and left eyes, respectively). The visual acuity improved from 0.36 logMAR to 0.25 logMAR when compared between the acute phase and the follow-up visit (p=0.003). Other clinical parameters (underlying

Table 2 Properties of patients examined or not examined by an ophthalmologist

	Ophthalmological examination	
	Yes	No
Total, n (%)	103	155
Male	56 (54)	84 (54)
Female	47 (46)	71 (46)
Mean age ±SD (years)	57±18*	63±17
Intensive care unit	13 (13)†	42 (27)
Abdominal malignancy	31 (30)	33 (21)
Leukaemia or lymphoma	5 (5)	15 (10)
Abdominal complication	30 (29)	43 (28)
Neurological or psychiatric	20 (19)	32 (21)
Injury	4 (4)	6 (4)
Alcohol abuse	4 (4)*	26 (17)
Intravenous drug	8 (8)	6 (4)
Central venous catheter	58 (54)	79 (51)
Autoimmune disease	3 (3)	9 (6)
Endovascular or valve prosthesis	3 (3)	5 (3)
Endocarditis	5 (5)	4 (3)
Death <3 months	3 (3)‡	55 (35)

Age and gender distribution are shown. In addition, conditions and properties associated with development of candidemia are presented. Those treated at intensive care units, patients suffering from alcohol-related complications or died within 3 months were less frequently examined by an ophthalmologist.
*P<0.01.
†P=0.05.
‡P<0.001.

disease, foreign body involvement and survival) for patients with OC are presented in table 3. More than half of the patients with OC, 58%, survived despite the concurred *Candida* BSI. There was no statistically significant difference in the mortality rate of the patients with *Candida* BSI with or without OC.

Effect of antifungal treatments on risk of OC

We explored the possibility that this choice of empirical antifungal treatment may affect development of OC (table 5). We also considered the possibility that the properties of the patients presented in tables 1 and 2 would associate with the risk of developing OC. We found that those with the most common underlying properties, CVC, or abdominal malignancy, appeared to have lower risk of OC when they were treated with echinocandin compared with those who received fluconazole (p=0.01). We also found that none of the patients without *C. albicans* who received echinocandin treatment developed OC.

Delay in antifungal treatment

We also evaluated the effect of delay in initiation of antifungal treatment on the risk of OC calculated from the time when the positive blood culture was drawn.

Table 3 A total of 103 patients were examined by an ophthalmologist

	Ocular candidiasis	
	Yes	No
Total, n (%)	33 (32)	70 (68)
Male	15 (46)	41 (59)
Female	18 (55)	29 (41)
Mean age ±SD (years)	55±13	61±19
Candida albicans	29 (88)*	44 (63)
C. glabrata	2 (6)	14 (20)
C. parapsilosis	0 (0)	6 (9)
Other *Candida* spp	2 (6)	6 (9)
No persisting blood culture (>72 hours)	16 (48)	49 (70)†
Intensive care unit	4 (12)	9 (13)
Abdominal malignancy	14 (42)	17 (24)
Leukaemia or lymphoma	4 (12)	1 (1)
Neutropenia (<0.1×10^9/L)	3 (9)	2 (3)
Abdominal complication	6 (18)	24 (34)
Neurological or psychiatric	4 (12)	16 (23)
Injury	1 (3)	3 (4)
Alcohol abuse	1 (3)	3 (4)
Intravenous drug	1 (3)	7 (10)
Central venous catheter (CVC)	21 (64)	37 (53)
CVC removal confirmed‡	15 (71)	28 (76)
Autoimmune disease	1 (3)	2 (3)
Endovascular or valve prosthesis	2 (6)	1 (1)
Endocarditis	0 (0)	5 (7)
Death <3 months	2 (6)	1 (1)
Alive >1 year	19 (58)	40 (57)

The table shows properties of those who had ocular candidiasis (n=33) compared with patients negative for ocular candidiasis (n=70). Conditions and properties related with development of candidemia are shown. Patients with *C. albicans* were more frequently affected. Patients in whom blood cultures were negative for candida during antifungal treatment (72 hours) had a lower number of ocular candidiasis.
*P<0.01.
†P=0.05.
‡Prompt removal of CVC was documented in 43 (74%) of 58 patient files.

Table 4 The table summarises the findings in patients with ocular candidiasis (OC)

	All *Candida*
	n=33
Bilateral OC	31 (94)
Chorioretinitis	31 (94)
Endophthalmitis	16 (48)
Chorioretinitis and endophthalmitis	14 (42)
Macula affected	22 (67)
Haemorrhages	12 (36)

Table 5 Effect of the timely empirical antifungal treatment (<12 hours) or delayed antifungal treatment (>12 hours) on positive (OC+) or negative (OC–) ocular candidiasis finding in relation with fluconazole or echinocandin treatment. In addition, association of the most common risk factors (presence of central venous catheter or abdominal malignancy) with positive or negative OC finding in relation with fluconazole or echinocandin treatment

Antifungal treatment	Fluconazole n (%)		Echinocandin n (%)	
OC	OC+	OC–	OC+	OC–
All *Candida* (n=101)	20 (19.8)	29 (28.7)	12 (11.8)	40 (39.6)
Treatment delay <12 hours (n=68)	14 (20.5)	18 (26.4)	9 (13.2)	27 (39.7)
Treatment delay >12 hours (n=29)	4 (13.7)	9 (31.0)	3 (10.3)	13 (44.8)
Central venous catheter (n=57)	15 (26.3)	14 (24.5)	6 (10.5)*	22 (38.6)
Abdominal malignancy (n=31)	11 (35.4)	7 (22.6)	2 (6.5)*	10 (32.2)
Candida albicans (n=73)	17 (23.2)	16 (21.9)	12 (16.4)	28 (38.3)
Treatment delay <12 hours (n=48)	12 (25.0)	9 (18.8)	9 (18.8)	18 (37.6)
Treatment delay >12 hours (n=22)	3 (13.6)	6 (27.2)	3 (13.6)	10 (45.4)
Central venous catheter (n=43)	15 (34.9)	7 (16.2)	6 (13.9)*	15 (34.9)
Abdominal malignancy (n=21)	9 (42.9)	4 (19.0)	2 (9.5)	6 (28.6)
Non-*albicans* (n=28)	3 (10.7)	13 (46.4)	0 (0)	12 (42.9)
Treatment delay <12 hours (n=20)	2 (10.0)	9 (45.0)	0 (0)	9 (45.0)
Treatment delay >12 hours (n=7)	1 (14.2)	3 (42.9)	0 (0)	3 (42.9)
Central venous catheter (n=15)	1 (6.7)	7 (46.7)	0 (0)	7 (46.7)
Abdominal malignancy (n=9)	2 (22.2)	3 (33.3)	0 (0)	4 (44.4)

*P<0.05.

However, no statistical difference in the number of OC was seen when we compared all cases with no delay with those who experienced a delay of 12 hours or longer in their antifungal treatment. In contrary, a significant benefit of early antifungal medication in the number of endophthalmitis was observed; those who received any antifungal medication within 12 hours had a lower number of endophthalmitis (n=14) when compared with cases with a delay of more than 12 hours (n=4, p<0.01).

Blood cultures during antifungal treatment

We looked for the possibility that patients in whom blood culture positivity persisted during antifungal treatment would be at higher risk of developing OC. We found that patients in whom blood cultures remained positive for *C. albicans* during antifungal treatment were at elevated risk of developing OC (p=0.02). These patients had more frequently CVC (p<0.001). We also observed that the *C. albicans*-positive patients who did not have CVC and who received early echinocandin treatment were less likely to have a persistent blood culture finding (p=0.05).

Endocarditis and OC

In our cohort, five cases of endocarditis with *C. albicans*-positive blood culture were confirmed and none of them developed OC. All these cases occurred in association with intravenous drug abuse. Mean age of patients with drug addiction was significantly lower (32 years vs 65 years, p<0.001) compared with the whole study population.

DISCUSSION

The incidence of OC in candidemia may range from 3% to 27%.[10] Ophthalmological consultation is recommended to all patients with candidemia[1–3 5] although some studies have failed to provide evidence supporting routinely performed ocular assessment.[1 4 11] Patients with candidemia are often severely ill and ophthalmological analysis may not be possible; in our study, OE was completed to the selected patients due to their critical condition. The examined patients appeared to be of younger age and healthier compared with those who were not examined (table 2). Patients at intensive care units, and those with alcohol-related conditions or poor prognosis, for example, were less frequently examined. Finally, 32% of the comprehensively examined patients in our study had ocular findings consistent with OC. It must be appreciated that the observed selection bias may have influenced our results. We believe that previous OC investigations are also based on selected patient material.

In agreement with the previous studies, the leading fungal isolate (88%) among our patients with OC was *C. albicans*.[3 5 12] We also found that those patients in whom blood cultures remained positive for *C. albicans* during antifungal treatment were at OC risk. Importantly, a shorter duration in persistence of candidemia was seen in echinocandin-treated patients with CVC. It is known that echinocandins can be active against *Candida* biofilm.[13] Evidence supporting the possibility that echinocandins can be more rapid in clearance of candidemia compared

with triazoles has also been presented.[14] It seems possible that efficient clearance of candidemia and activity against *Candida* biofilm may protect from developing eye complications in candidemia.

Early treatment with any antifungal medication reduced the number of endophthalmitis; those who received either fluconazole or echinocandin within 12 hours had a lower number of endophthalmitis when compared with cases with a delay of more than 12 hours ($p<0.01$). However, a delay in antifungal treatment was not associated with an increase in chorioretinitis when the entire study population was considered. In addition, no advantage of fluconazole, a drug of choice in intraocular *C. albicans* infections, was seen. First-line use of echinocandin with low intraocular concentration appeared favourable compared with fluconazole at least in patients with CVC or abdominal malignancy. Interestingly, none of the patients without *C. albicans* who received echinocandin developed OC. This is in line with the recent study that reported no increased ocular involvement in patients with *Candida* BSI initially treated with echinocandins.[15]

Lack of CVC in association with echinocandin treatment protected from persistent candidemia in our study. This result highlights the importance of prompt CVC removal in candidemia. It is also known that persisting blood cultures can be seen in endocarditis.[16 17] Although we completed echocardiography to a high proportion of our patients, none of the patients with endocarditis with *C. albicans* BSI developed OC. It seems possible that the young age of our patients with endocarditis protected them from OC. This is supported by the fact that risk of OC in our study was significantly lower in those below 40 years of age compared with the whole patient population. Apparently, routine echocardiography may not be necessary to identify those at OC risk. The ophthalmological assessment for OC might thus be justified by the overall risk profile of a patient.

Early appropriate antimicrobial treatment improves prognosis of patients with *Candida* BSI.[18–20] In our study, an early initiation of antifungal medication reduced the risk of endophthalmitis. Time between the positive blood culture and initial OE can affect the OC rate.[3 21] Diagnostic findings in endophthalmitis, for example, may require several days to develop.[10] Ophthalmological methods and extent of evaluation can be variable in studies involving OC in candidemia. Cooperation required for reliable OE may not be possible in intensive care settings; priority must be given to life-saving treatments in critical conditions. In conclusion, the selection of patients referred to ophthalmologists, timing of OE and the used methods may affect the reported frequencies.

In summary, our study based on careful ocular biomicroscopy analysis of patients with candidemia provides evidence supports the view that choice and timing of the first-line antifungal treatment affects the risk of ocular complications. It must be noted, however, that we evaluated the possibility of preventing OC by the choice of antifungal medication. Our results, however, do not provide information on the optimal OC treatment. Still, early treatment with any antifungal agent and echinocandin treatment in selected cases may protect the patients with candidemia from developing OC.

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