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Impact of routine bedside infectious diseases service on clinical management and prognosis of patients with *Candida* fungemia – an example for Antifungal Stewardship at university level in Germany

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ABSTRACT

Background: Candidemia is rare and has a high mortality rate. This study analyses the impact of bedside antifungal stewardship (AFS) on clinical management and prognosis of patients with candidemia at a university hospital in Germany.

Methods: All patients with at least one positive blood culture with *Candida* species between 2014 and 2016 received bedside AFS with standardized recommendations. Medical records were retrospectively analyzed. Results from the intervention period from 2014-2016 (n=109), with focus on 2016 (n=39), were compared with those from the pre-intervention period in 2013 (n=30).

Results: Bedside AFS was performed in 24/35 (69%) surviving patients in 2016 within the first 3 days after diagnosis of candidemia. All surviving patients (n=35) in 2016 received antifungal treatment compared with 24/28 (86%) in 2013 (p=0.0344). Follow-up blood cultures were performed in 25/35 (71%) in 2016 compared with 10/25 (40%) in 2013 (p=0.0046). Survival in the intervention compared with the pre-intervention group did not differ significantly (p=0.58) one year after the diagnosis of candidemia was made. However, patients with candidemia often have multiple serious comorbidities.

Conclusions: Individualized bedside AFS significantly improves adherence to recommendations for patients with *Candida* fungemia, especially guideline-oriented diagnostics and therapy. Improving the prognosis of patients with candidemia remains a huge challenge for AFS.

INTRODUCTION

Systemic fungal infections occur much less frequently than bacterial bloodstream infections (Niederman et al., 2021). However, invasive candidiasis is an increasingly important nosocomial infection in both adults and children (Lamoth et al., 2018), and mortality may affect almost two-thirds of patients (Bougnoux et al., 2008).

Diagnosis and treatment of candidemia is complex. It is rather unusual that patients suspected of having a systemic infection will immediately receive antifungal treatment except for patients with abdominal complications such as intestinal perforation or patients at the intensive care unit (ICU) (Martin-Loeches et al., 2019). This indicates that most patients usually do not receive an antifungal agent at the time of systemic fungal infection diagnosis.

The detection of *Candida* species (spp.) in blood culture (BC) should not be misinterpreted as contamination until proven otherwise (Hall and Lyman, 2006). However, clinical experience shows that clinicians often mistakenly make this assumption. There is a need to immediately start antifungal treatment because any delay worsens prognosis in patients with a systemic fungal infection (Lortholary et al., 2014, Morrell et al., 2005). Although there are a number of available national (Groll et al., 2020), European (Cornely et al., 2012), and international (Pappas et al., 2016) clinical guidelines for the management of candidemia, adherence is considered low (Mellinghoff et al., 2018). One of the reasons might be lacking knowledge about existing guidelines for specific infections such as candidemia.

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In *Staphylococcus aureus* bacteremia, it has been shown that a bedside infectious disease (ID) consultation and direct discussion of the treatment with the clinician is one of the most important steps to provide optimal treatment, perform further adequate diagnostic steps, and improve survival. A telephone call alone is not sufficient (Forsblom et al., 2013).

Routine bedside ID service in the form of antifungal stewardship (AFS) consultation can increase the adherence to clinical guidelines (Mejia-Chew et al., 2019, Murakami et al., 2018, Ruhnke, 2014) and awareness of candidemia. However, bedside ID service is time-consuming, and the effect is rather short lasting as junior physicians are frequently on rotations. Continuous AFS is needed for further improvements in patient care.

The importance of AFS is often underestimated because, compared with antibiotic stewardship (ABS)/antimicrobial stewardship for bacterial diseases, the positive effects in the affected patients can rarely be clearly identified. In addition, the positive collateral effects of AFS on the treatment of patients with infectious diseases are usually not even considered (Hart et al., 2019).

This study analyses the impact of routine bedside AFS on clinical management and prognosis of patients with culture-proven candidemia at the University Medical Center in Göttingen (UMG), a university hospital with maximum care in Germany.

PATIENTS AND METHODS

Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the UMG (Germany 13/4/13, 17 July 2013).

Study site

The UMG is a maximum care hospital with 1,450 admission beds. A total of 67 clinics, institutes, and departments take care of approximately 65,000 admitted patients and 225,000 outpatients annually.

Study population

Medical records were retrospectively analyzed by two investigators (AD and MHS) independently from each other. Differing information was discussed and consensus was reached.

A case of candidemia was defined as a patient with *Candida* spp. found in at least one BC. All UMG patients admitted from 2013 to 2016 with candidemia were included in the study. Our intervention started in 2014. Patients with candidemia in 2013 were the pre-intervention control group, and patients with candidemia from 2014 to 2016, especially from the last year of intervention—2016, were our intervention group. Four patients with *Cryptococcus* spp.–positive BCs were excluded.

Antibiotic and Antifungal Stewardship

In 2012, ABS was started at the UMG and has since been an integral part of clinical patient care. The interdisciplinary ABS team consists of clinical microbiologists, pharmacists, an ID specialist, representatives of clinical departments (e.g., internal medicine), and a representative from laboratory medicine. Important components of ABS at the UMG are as follows: infectious disease counseling by telephone; weekly infectious diseases ward rounds with discussion of appropriateness of prescribed anti-infectives; bedside consultation of patients with infectious diseases caused by multiresistant pathogens; department-specific training on infectious diseases and their diagnostics and up-to-date therapy; preparation of department-specific guidelines for prophylactic, empirical, and targeted anti-infective therapy of infectious diseases; diagnostic stewardship; and organization of activities for the annual European Antibiotic Awareness Day. Owing to the increasing importance of systemic fungal infections, bedside AFS was started at the UMG in 2014 as part of ABS to further support clinicians in the management and treatment of patients with suspected and culture-proven systemic fungal infection.

Microbiological analysis

A pair of BC bottles (aerobic-BACT/ALERT® FN Plus/anaerobic-BACT/ALERT® FA Plus; bioMérieux, Durham, USA) was cultivated for 5 days in the automated blood culture system BACT/ALERT® 3D (bioMérieux, Marcy-l'Étoile, France). After a positive signal indicating growth, a Gram stain was made, and in the case of microscopic evidence of yeasts, the following subcultures were done: i.) on two Columbia blood agar plates (bioMérieux, Nürtingen, Germany), incubated aerobically and anaerobically, respectively; ii.) on one chocolate agar plate (bioMérieux, Nürtingen, Germany), incubated in CO_2-enriched atmosphere; iii.) on one Sabouraud-glucose + gentamicin + chloramphenicol agar plate (Oxoid GmbH, Wesel, Germany), incubated aerobically. Plates were incubated for 24 to 48 hours at 36 ± 1°C. Species identification was performed using MALDI Biotyper 3.0 (Bruker Daltonics, Bremen, Germany) (Bader, 2013). Antimicrobial susceptibility testing was based on the VITEK 2 (bioMérieux, Marcy-l'Étoile, France) using AST-YS08.

Intervention and interdisciplinary approach

Routine bedside ID service (intervention) for candidemia provided by the ABS team of the UMG started in 2014 and is referred to as AFS. This interdisciplinary team consists of a clinical microbiologist, an ID specialist, and a pharmacist.

The microscopical detection of yeast in the Gram stain is reported immediately through the microbiologist on duty, who might also be an AFS team member, i.) first to the patientś clinician by phone and ii.) second to the AFS team (clinical microbiologist and/or ID specialist) by phone or email. The microbiologist on duty or the AFS team member recommends initiation of antifungal treatment (Clinical Approach B, Figure 1), whereas the AFS team members almost exclusively discuss an already ongoing antifungal treatment (Clinical Approach A, Figure 1) and give the recommendation to immediately collect at least two follow-up BC pairs, to perform a transesophageal echocardiography and a fundoscopy, and to change the intravascular catheters promptly, respectively. Further follow-up BCs are collected as long as follow-up BCs again shows growth of *Candida* spp.

As soon as possible, an on-site consultation at the ward is done, and the patient is attended by the clinical microbiologist or the ID specialist, often accompanied by the pharmacist who checks for possible drug interactions and comments on the dosage of antifungal therapy, if not on-site, then by a phone call.

Antifungal treatment

The collection date of the first negative follow-up blood culture is the start date of the 14-day antifungal therapy according to the guidelines (Cornely et al., 2012, Groll et al., 2020, Pappas et al., 2016).

In case of the Clinical Approach A (Figure 1), the doctor in charge usually prescribes the patient an empirical antifungal treatment with an echinocandin (e.g., caspofungin) or an azole (e.g., fluconazole) according to the departmental guideline.

In case of the Clincal Approach B (Figure 1), the clinical microbiologist or ID specialist recommends an echinocandin (e.g., caspo-

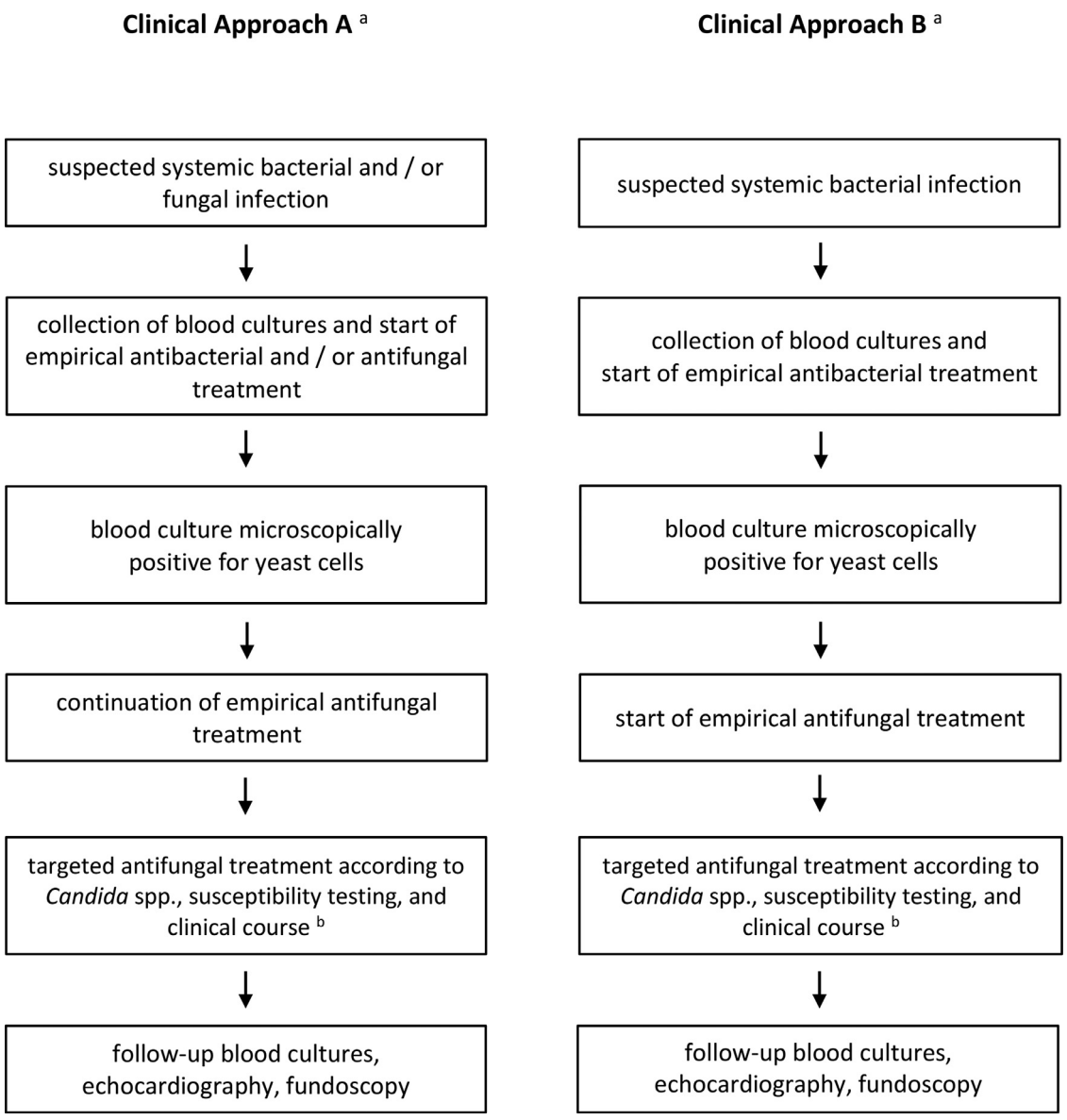

Figure 1. Clinical approach to patients with blood culture-proven candidemia
[a]Antifungal stewardship provides proactive support independent of clinicianś request at least at the following times: i.) when microscopy of the positive BC is known; ii.) when the final results of the BC are ready with known *Candida* spp. and antifungal susceptibility.
Regardless of this, clinicians have the option of contacting the antifungal stewardship team by phone during regular duty hours from 8:00 a.m. to 4:30 p.m., Monday through Friday, if needed. In addition, the physician on call of the Institute for Medical Microbiology and Virology can be reached by telephone around the clock outside regular duty hours, on weekends and holidays.
[b]In case of a favorable clinical course (clinical improvement with termination of or decreasing vasopressor therapy and normalization of inflammatory markers like leucocyte count, C-reactive protein and procalcitonin) along with clearance of BC and a fluconazole-susceptible *Candida* isolate in the antifungal susceptibility testing, a switch from echinocandin to fluconazole therapy was preferred.

fungin or anidulafungin) or an azole (e.g., fluconazole), in case of detection of yeast cells in the gram-stained blood smear.

After *Candida* spp. identification, antifungal treatment is adapted in both approaches according to the detected *Candida* spp., antifungal susceptibility testing, and clinical course.

Statistical analysis

Statistical analysis was done using STATISTICA, version 10, for Windows (StatSoft GmbH, Hamburg, Germany). Comparisons between groups were performed using Student's t-test for continuous data and chi square or Fisher's exact test for categorical data. P-values were regarded as significant at <0.05. Kaplan–Meier method was applied to assess survival probabilities and therapy times graphically, and comparison was made using a two-sided log-rank test, both performed with R (RCoreTeam, 2022; https://www.R-project.org/).

RESULTS

Detected Candida *spp. in blood cultures*

Table 1 shows the number of patients, the spectrum of *Candida* spp. found in BCs, and the number of candidemia cases/1,000 admissions from 2013 to 2016 at the UMG.

Table 1
Number of patients and spectrum of detected *Candida* spp. in blood cultures, 2013-2016.

	2013[a]	2014[b]	2015[b]	2016[b]
Candida albicans	17	20	22	25[c,d]
Candida glabrata	6	6	8	10[c]
Candida tropicalis	3	2	2	3
Candida parapsilosis	3	1	6	3
Candida krusei	1	0	1	1 [d]
Candida dubliniensis	0	1	0	0
Candida pelliculosa	0	1	0	0
Candida kefyr	0	0	0	1
Total no. of *Candida* spp.	30	31	39	43
Total no. of patients	30	31	39	39
No. cases / 1,000 admissions	0.51 [e]	0.51 [e]	0.62 [e]	0.61[e]

[a] Pre-intervention period.
[b] Intervention period.
[c] Three double infections with *C. albicans* and *C. glabrata.*
[d] One double infection with *C. albicans* and *C. krusei.*
[e] Admissions: 2013—59,147; 2014—61,088; 2015—63,136; 2016—64,412.

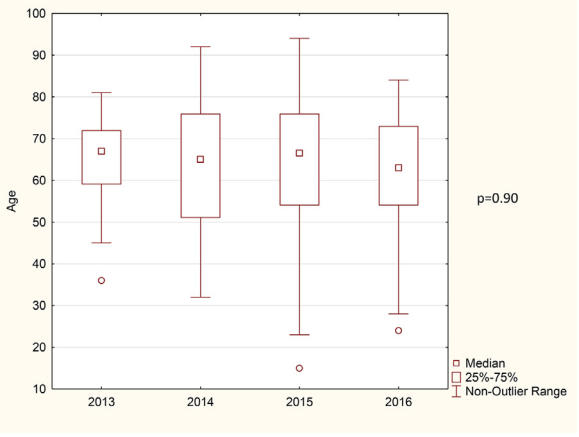

Figure 2. Box plot of ages in pre-intervention (year 2013) and intervention group (years 2014 to 2016).

C. albicans was the most frequently identified *Candida* spp. followed by *C. glabrata*. The proportions of the *Candida* spp. in each year did not change significantly in the study period.

Infection with more than one *Candida* spp. occurred in four patients only in the year 2016.

Bacterial species detected in addition to Candida *spp. in blood cultures*

In addition to *Candida* spp., pathogenic bacterial species were found in 12/139 (8.6%) patients (Supplementary Table 1). Most frequently, *Enterococcus faecium* (n=5) and *Staphylococcus aureus* (n=3) were detected. Co-infection with more than one bacterial species occurred in two patients.

Acquisition of candidemia, comorbidities, and risk factors

Figure 2 shows the age of both groups displayed in box plots. Table 2 contains the mode of acquisition, comorbidities, and other risk factors. Patients in the intervention period i.) suffered significantly less frequently from diabetes without complication, solid tumors without metastasis, wound infection, and dysphagia and ii.) received significantly more transfusions, total parenteral nutrition, and previous antibiotics.

Among the top 10 comorbidities and risk factors in the pre-intervention and intervention group were pneumonia, acute kidney failure, sepsis and septic shock, central venous catheter, mechanical ventilation, urinary catheter, and transfusion.

Diagnosis of candidemia was most often made in patients admitted to the ICU or intermediate care unit: 2013 (pre-intervention)—17/30, 57%; compared to intervention years 2014—24/31, 77%, p=0.8748; 2015—27/39, 69%, p=0.2817; 2016—22/39, 56%, p=0.9830.

Antifungal stewardship

Table 3 shows the time frame of phone call AFS and bedside AFS in 2016, the last year of intervention. Clinicians received a phone call AFS before a bedside AFS was performed for 26/35 (74%) patients. For 4/35 (11%) patients, clinicians received only a phone call AFS because these patients were on palliative management (one patient), discharged (one patient), transferred to another hospital (one patient), or already deceased (one patient). For 6/35 (17%) patients, clinicians received only bedside AFS.

Antifungal treatment

Table 4 contains detailed information about antifungal treatment in patients with candidemia in 2013 (pre-intervention) and 2016 (last year of intervention). It is of note that in 2016, all patients who were surviving with diagnosed candidemia 35/35 received antifungal treatment compared with 24/28 in 2013 (p=0.0344).

In 2013, 3/10 (30%) patients were given antifungal therapy for at least 14 days after negative follow-up BCs compared with 10/25 (40%) patients in 2016 (p=0.7094). The cause of a shorter antifungal therapy was an early death of the patient in 2/10 (20%) patients in 2013 compared with 4/25 (16%) patients in 2016 (Figure 3).

Figure 4 shows the therapy times with Kaplan–Meier curves for 2013 (pre-intervention) and 2016 (last year of intervention), which did not differ significantly (p=0.7300).

Diagnostics

The number of BC pairs taken at the first sampling time was generally higher at ICUs—2013: 2.2; 2016: 2.6—compared with normal wards—2013: 1.8; 2016: 1.5.

Follow-up BCs were taken from 10/28 (36%) patients in 2013 compared to 25/35 (71%) in 2016 (p=0.0046) (Figure 3).

An echocardiographic examination was performed in 5/28 (18%) patients in 2013 compared with 12/35 (34%) in 2016 (p=0.1443) and a fundoscopy in 2/28 (7%) patients in 2013 compared with 10/35 (29%) in 2016 (p=0.0313).

Survival and mortality

Figure 5 shows the survival by Kaplan–Meier curves of the pre-intervention (year 2013) and intervention groups (years 2014 to 2016), which did not differ significantly (p= 0.5800). Table 5 contains mortality details for each year.

DISCUSSION

Candidemia remains a rare disease despite its increasing importance as a nosocomial infection. Detection of *Candida* spp. in a BC should never be considered as a contaminant and must always trigger the immediate start of antifungal treatment and the search for the source of infection (Morrell et al., 2005).

Diagnosis of candidemia is challenging and it is an important task for AFS to improve diagnostics. Invasive candidiasis encompasses candidemia and deep-seated candidiasis. Deep-seated candidiasis may lead to secondary candidemia but not necessarily (Clancy and Nguyen, 2013). BC remains the gold standard for diagnosis of candidemia (Pappas et al., 2018). However, BCs will not

TABLE 2
Acquisition of candidemia and patient characteristics.

	Pre-intervention[a] n=30	Intervention[b] n=109	p[c]
Acquisition			
Community-acquired	-	2	
Nosocomial	29	95	
OPD during last 3 months	-	2	
Admitted during last 3 months	1	10	
Female gender	8 (26.7%)	46 (42.2%)	0.1221
Comorbidities			
Coronary vascular disease	9 (30.0%)	25 (23.0%)	0.4254
Myocardial infarction	7 (23.3%)	13 (12.0%)	0.1149
Congestive heart failure	12 (40.0%)	32 (29.4%)	0.2671
Peripheral vascular disease	3 (10.0%)	14 (12.8%)	1.0000
Cerebrovascular disease	5 (16.7%)	23 (21.1%)	0.5918
Hemi-/paraparesis /-plegia	4 (13.3%)	16 (14.7%)	1.0000
Dementia	3 (10.0%)	4 (3.7%)	0.1714
COPD	3 (10.0%)	23 (21.1%)	0.1972
Connective tissue disease	4 (13.3%)	15 (13.8%)	1.0000
Ulcus disease	0	6 (5.5%)	0.3402
Liver disease Child A	0	1 (0.9%)	1.0000
Liver disease Child B or C	1 (3.3%)	3 (2.8%)	1.0000
Diabetes without complications	8 (26.7%)	12 (11.0%)	0.0305
Diabetes with complications	2 (6.7%)	5 (4.6%)	0.6439
Kidney disease without dialysis	6 (20.0%)	24 (22.0%)	0.8119
Kidney disease with dialysis	1 (3.3%)	8 (7.3%)	0.6837
Solid tumor without metastasis	9 (30.0%)	14 (12.8%)	0.0251
Solid tumor with metastasis	5 (16.7%)	30 (27.5%)	0.2250
Lymphoma	1 (3.3%)	4 (3.7%)	1.0000
Hematologic malignancy	1 (3.3%)	3 (2.8%)	1.0000
Stem cell transplantation	2 (6.7%)	1 (0.9%)	0.1175
Organ transplantation	1 (3.3%)	1 (0.9%)	0.3863
HIV	0	1 (0.9%)	1.0000
Pneumonia	19 (63.3%)	65 (59.6%)	0.8338
Empyema	3 (10.0%)	6 (5.5%)	0.4055
ARDS	4 (13.3%)	14 (12.8%)	1.0000
Sepsis	16 (53.3%)	73 (67.0%)	0.1681
Septic shock	14 (46.7%)	46 (42.2%)	0.6620
Endocarditis	1 (3.3%)	4 (3.7%)	1.0000
Wound infection	8 (26.7%)	7 (6.5%)	0.0016
Prosthetic infection	3 (10.0%) [d]	2 (1.8%) [e]	0.0672
Spondylodiscitis	1 (3.3%)	2 (1.8%)	0.6170
Urinary tract infection	8 (26.7%)	38 (34.9%)	0.3982
Acute kidney failure	17 (56.7%)	54 (49.5%)	0.4893
Acute liver failure	5 (16.7%)	17 (15.6%)	0.8869
Hyperlipidemia	6 (20.0%)	17 (15.6%)	0.5654
Hyperuricemia	1 (3.3%)	6 (5.5%)	1.0000
Pancreatitis	5 (16.7%)	9 (8.3%)	0.1753
Cholecystitis	2 (6.7%)	11 (10.1%)	0.7341
Peritonitis	5 (16.7%)	22 (20.2%)	0.6664
Intraabdominal infection not specified	4 (13.3%)	11 (10.1%)	0.7394
Ileus	9 (30.0%)	18 (16.5%)	0.0983
Bowel rupture	1 (3.3%)	9 (8.3%)	0.6898
Hematoma	4 (13.3%)	5 (4.6%)	0.1008
Gastrointestinal bleeding	3 (10.0%)	19 (17.4%)	0.4077
Dysphagia	16 (53.3%)	18 (16.5%)	0.0000
Dysarthria/aphasia	1 (3.3%)	4 (3.7%)	1.0000
Epilepsy	4 (13.3)	7 (6.4%)	0.2515
Polyneuropathy	6 (20.0%)	14 (12.8%)	0.3223
Cachexia	2 (6.7%)	18 (16.5%)	0.2442
Neutropenia	2 (6.7%)	10 (9.2%)	1.0000
Coagulation disorder	13 (43.3%)	53 (48.6%)	0.6074
Risk factors			
Mechanical ventilation	21 (70.0%)	71 (65.1%)	0.6181
Cardiac surgery	4 (13.3%)	20 (18.4%)	0.5982
Abdominal surgery	14 (46.7%)	39 (35.8%)	0.2769
Transfusion	18 (60.0%)	89 (81.7%)	0.0126
Total parenteral nutrition	1 (3.3%)	22 (20.2%)	0.0271
Enteral nutrition	4 (13.3)	8 (7.3%)	0.2891
Central venous catheter	26 (86.7%)	87 (79.8%)	0.3942
Port	5 (16.7%)	30 (27.5%)	0.2251
Arterial catheter	13 (43.3%)	45 (41.3%)	0.8403
Urinary catheter	19 (63.3%)	60 (55.1%)	0.4171
Steroids	2 (6.7%)	6 (5.3%)	0.6825
Previous antibiotics	9 (30.0%)	81 (74.3%)	0.0000
Previous antifungal treatment	2 (6.7%)	10 (9.2%)	1.0000
Colonization with MRSA	3 (10.0%)	9 (8.3%)	0.7217
Colonization with MRGN	3 (10.0%)	8 (7.4%)	0.7031
Colonization with VRE	0	5 (4.6%)	0.5849

Data are expressed as n (%) of patients
Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; MRGN, multidrug resistant gram-negative bacteria; MRSA, methicillin resistant *Staphylococcus aureus*; OPD, out-patient department; VRE, vancomycin resistant *Enterococcus faecium.*
[a] Year 2013.
[b] Years 2014 – 2016.
[c] Chi square test or Fisher's exact test.
[d] One pacemaker infection, two infections of knee endoprosthesis.
[e] One pacemaker infection, one infection of aortic bifurcated bypass graft.

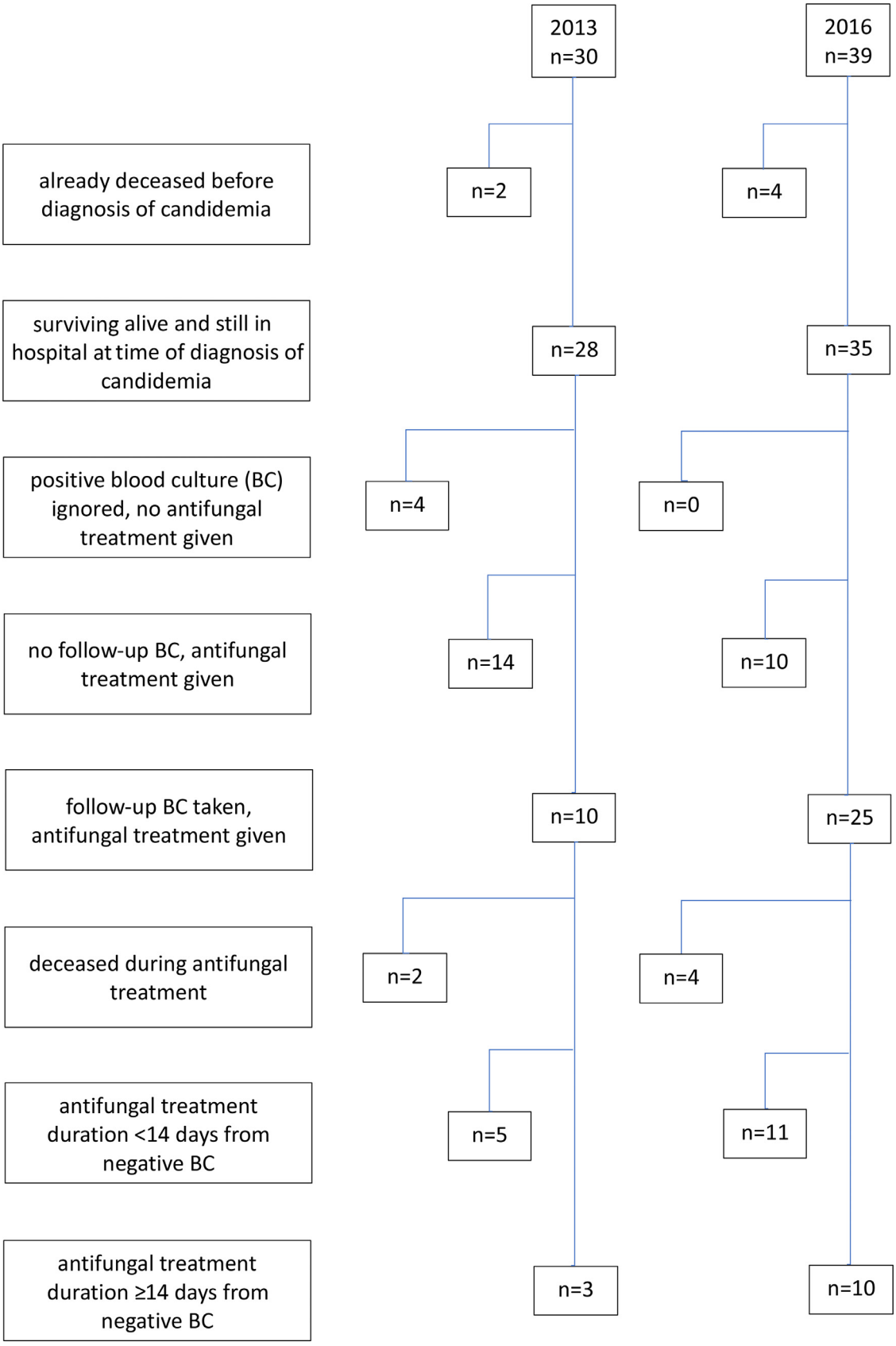

Figure 3. Patient flow chart: implementation of follow-up blood cultures and duration of antifungal treatment.

Table 3
Time frame of antifungal stewardship in patients with candidemia in 2016.

Time after known candidemia	Cumulative number of patients who received an AFS phone call before bedside AFS[a]	Cumulative number of patients who received bedside AFS[a]
Day 0	17/35 (49%)	9[b]/35 (26%)
Day 1	23/35 (66%)	14/35 (40%)
Day 2	26/35 (74%)	22/35 (63%)
Day 3	27/35 (77%)	24/35 (69%)
Day 4	27/35 (77%)	26/35 (74%)
Day 5	27/35 (77%)	28/35 (80%)
Day 6	27/35 (77%)	28/35 (80%)
Day 7	29/35 (83%)	28/35 (80%)
Day 8	29/35 (83%)	30/35 (86%)

AFS, antifungal stewardship.
[a] 4/39 patients in 2016 died ≤48h before *Candida* spp. was detected in BC.
[b] 8/9 patients already received an AFS phone call before bedside AFS on the same day.

diagnose deep-seated candidiasis that is not associated with candidemia. This must be considered when evaluating the diagnostic value of BCs in invasive candidiasis, otherwise the value of BCs is estimated to be lower than the actual value (Clancy and Nguyen, 2013).

Data about fungal concentration in blood of patients with candidemia are from studies in which lysis-centrifugation BC systems (Dorn and Smith, 1978) were used for detection. In these studies, fungal densities of less than 1 colony-forming unit (CFU)/mL were observed in about half of the patients (Bille et al., 1984, Henry et al., 1983, Kiehn, 1989, Kiehn et al., 1983). Meanwhile, continuous-monitoring automated BC systems are widespread. The culture media used here are among the most fertile broth media used in clinical microbiology. Nevertheless, inadequate sampling volumes will remain a critical factor hampering microorganism recovery (Lamy et al., 2016). Therefore, it is necessary that BC collection follows a standardized strategy. The classical multisampling strategy with collection of only one pair of BC (one aerobic and

Table 4
Antifungal treatment and diagnostics in patients with candidemia in 2013 (pre-intervention) and 2016 (last year of intervention).

	2013 pre-intervention period (n=30)	2016 last year of intervention (n=39)	p
Start of AFT			
No AFT despite known candidemia	4/28[a]	0/35[a]	0.0344
Already ongoing AFT when BCs were taken	3/30[b]	6/39[b]	0.5103
Start of AFT on day when BCs were taken	4/30	4/39	0.6922
Start of AFT after candidemia was known	16/28[a]	26/35[a]	0.1514
Total AFT duration (days) irrespective of follow-up blood cultures	18.46±12.08	18.31±15.97	0.7300
Initial AFT			
Fluconazole iv	10/24	13/36	0.6646
Fluconazole oral	3/24	1/36	0.1391
Voriconazole iv	1/24	-	
Caspofungin iv	9/24	22/36	0.0730
Liposomal amphotericin B iv	1/24	-	
First AFT switch			
Azole to echinocandin	4[c]	5[c]	
Echinocandin to azole	5[d]	6[d]	
Echinocandin to liposomal amphotericin B	1[e]		
Second AFT switch			
Azole to echinocandin	2[f]	1[f]	
Echinocandin to azole	1[g]	-	
IV to oral AFT switch	4[h]	5[h]	
follow-up blood cultures	10/28	25/35	0.0046
Central venous catheter (implanted port not included)			
Central venous catheter(s) not removed	5/23	3/15	0.8977
Not all central venous catheter(s) removed	1/23[i]	0/15	1.0000
Central venous catheter(s) removed	17/23	12/15	1.0000
Implanted port			
Port not removed	4/5	8/15	0.6027
Port removed	1/5	7/15	0.6027
Time of central line / ports removal			
on day when positive BCs were taken	5/18	9/19	
≤48h after positive BCs were taken	5/18	4/19	
>48h - ≤7d after positive BCs were taken	6/18	4/19	
>7d after positive BCs were taken	2/18	2/19	
Central venous catheter microbiology	12/18	17/19	
Detection of *Candida* spp. on central line	8/12	13/17	
Echocardiography	5/28	12/35	0.1443
Ophthalmological consultation / fundoscopy	2/28	10/35	0.0313

AFT, antifungal treatment; BC, blood culture; IV, intravenous.
[a] 2/30 patients in 2013 and 4/39 patients in 2016 died ≤48h before *Candida* spp. was detected in BC; one of these four patients in 2016 was started on AFT after initial BC were taken.
[b] 2013 – 1x fluconazole, 1x caspofungin, 1x liposomal amphotericin B; 2016 - 3x fluconazole, 3x caspofungin.
[c] 2013 – candidemia through *C. albicans* 3x, *C. tropicalis* 1x; 2016 – candidemia through *C. albicans* 1x, *C. glabrata* 3x, *C. tropicalis* 1x.
[d] 2013 – candidemia through *C. albicans* 2x, *C. glabrata* 1x; 2016 – candidemia through *C. albicans* 3x, *C. glabrata* 1x, *C. parapsilosis* 2x.
[e] 2013 – candidemia through *C. albicans* 1x.
[f] 2013 – candidemia through *C. albicans* 1x, *C. krusei* 1x; 2016 – candidemia through *C. albicans* 1x.
[g] 2013 – candidemia through *C. albicans* 1x.
[h] 2013 – candidemia through *C. albicans* 2x (fluconazole oral 1x, voriconazole oral 1x), *C. glabrata* 1x (fluconazole oral), *C. parapsilosis* 1x (fluconazole oral); 2016 – candidemia through *C. albicans* 5x (fluconazole oral 4x, voriconazole oral 1x).
[i] Only one of two central venous catheters removed.

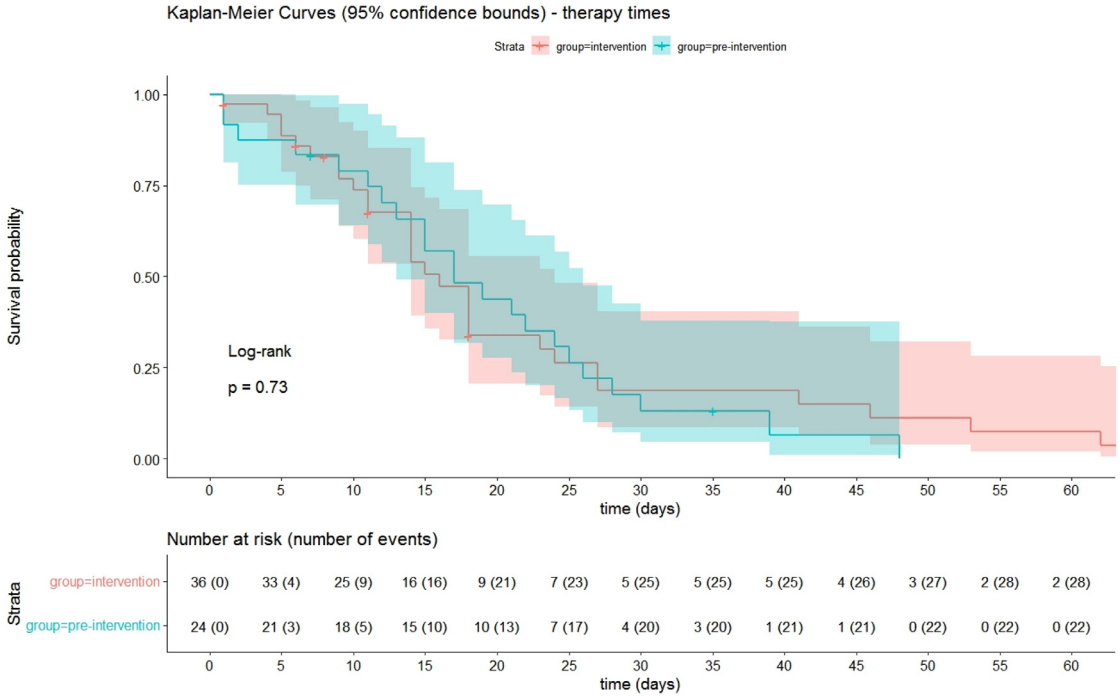

Figure 4. Kaplan–Meier curves showing therapy times in 2013 (pre-intervention) and 2016 (last year of intervention)

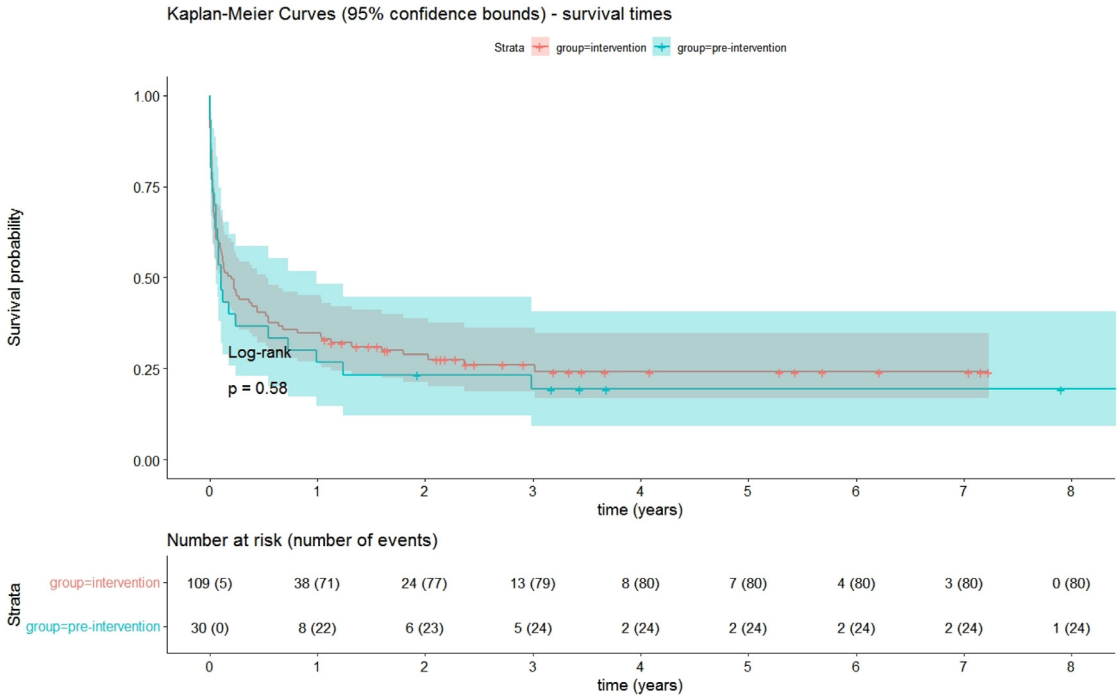

Figure 5. Kaplan–Meier curves showing survival times of pre-intervention (year 2013) and intervention groups (years 2014 to 2016)

Table 5
Mortality in patients with candidemia

	Mortality day 30	day 90	day 180	day 365
2013	13/30 (43%)	18/30 (60%)	18/30 (60%)	22/30 (73%)
2014	13/31 (42%)	15/31 (48%)	18/31 (58%)	19/31 (61%)
2015	15/39 (38%)	21/39 (54%)	23/39 (59%)	26/39 (67%)
2016	16/39 (41%)	23/39 (59%)	24/39 (62%)	26/39 (67%)
2014-2016	44/109 (40%)	59/109 (54%)	66/109 (61%)	71/109 (65%)
	p=0.7698[a]	p=0.5666[a]	p=0.9564[a]	p=0.3982[a]

[a] 2014-2016, intervention group, compared to 2013, pre-intervention group.

one anaerobic bottle) at different times might fail to detect candidemia because usually only one aerobic bottle will be filled with 8 to 10 ml of blood at one time. Therefore, we prefer the single sampling strategy collecting 60 ml of blood at one time, filling three aerobic bottles each with 10 ml of blood (Lamy et al., 2016). The diagnostic stewardship training of clinicians to implement an optimal BC collection strategy is an important task of the AFS team at the UMG. It might contribute in discovering patients with candidemia who would have previously remained undetected because of the low pathogen concentration in the blood. Patients with candidemia may also be diagnosed at an earlier stage of the disease, leading to improved survival and thus better prognosis (Salm et al., 2018).

What real importance polymerase chain reaction–based tests for the detection of fungal infections will have in daily routine in the future remains to be seen (Clancy and Nguyen, 2018, Pappas et al., 2018). Our experience at the UMG is still limited.

Study results concerning mortality due to *Candida* spp. are difficult to compare (Arendrup et al., 2011, Lortholary et al., 2014) and show some considerable differences.

Antimicrobial stewardship without an ID specialist could not change the 30-day mortality (Murakami et al., 2018), which was about 23% in the pre-intervention and intervention groups. However, recent studies show that an ID consultation lowers mortality in patients with candidemia. In the study by Lee et al., 30-day mortality was reduced from 50% to 20% and 60-day mortality was reduced from 59% to 24% (Lee et al., 2019). In the study by Mejia-Chew et al., 90-day mortality decreased from 51% to 29% (Mejia-Chew et al., 2019).

In our study, neither 30-day mortality nor one-year mortality showed a difference between the pre-intervention (year 2013) and intervention (year 2014-2016) group (43% compared with 40%, p=0.7698, and 73% compared with 65%, p=0.3982; Table 5), as previously found in some studies (Mellinghoff et al., 2018, Rac et al., 2018). Kaplan–Meier curves of survival in the intervention group compared with the pre-intervention group did not differ significantly (p=0.58) one year after the diagnosis of candidemia was made in our study.

Patients in the intervention group of our study received more transfusions (p=0.0126) and had previous exposure to antibiotics more frequently (p=0.0000). This could be a hint that patients in the intervention group had a more serious course of candidemia due to severe comorbidities. Increasing evidence shows the pre-eminent role of the underlying conditions on survival (Lortholary et al., 2017). The number of patients with more severe comorbidities is increasing, making them more prone to have systemic fungal infections irrespective of new treatments and recommendations (Bretagne et al., 2021).

Finally, patients treated at a maximum care hospital are always a highly selected group of patients frequently with many comorbidities, are often transferred from other hospitals, and have already received some pretherapies for communicable and noncommunicable diseases.

Central venous catheter management in patients with candidemia is considered to be an important issue. Cleveland et al. reported a significant decline in the overall incidence of candidemia in two US metropolitan regions, especially among cases with a central venous catheter, and explained it as the result of policies and practices related to catheter insertion and maintenance. However, it needs to be mentioned that US policies incentivize reducing central line-associated bloodstream infections (Cleveland et al., 2015). Until now, there has been no randomized clinical trial providing evidence that early or late catheter removal improves prognosis among patients with candidemia (Janum and Afshari, 2016).

The increasing number of patients with an implanted port in 2016 in our study is striking. These are almost exclusively patients receiving chemotherapy for malignant disease. Perhaps this could also be seen as a marker of increasingly sicker patients.

Treatment of any infection remains a physician-driven choice and reflects real-world clinical practice (Mejia-Chew et al., 2020). There is a need for high level of suspicion to start empirical antifungal treatment right at the point of BC collection. What counts here is simply clinical experience. A potential risk factor for candidemia mortality is delaying empirical treatment until positive BC results are received (Morrell et al., 2005).

However, improving the prognosis of patients with candidemia remains a huge challenge for AFS.

Our study may have some limitations. Patient records were examined retrospectively. Only well-documented patient characteristics, comorbidities, and risk factors were available for statistical analysis, but medical records could have been lacking some data or may have been incomplete. In addition, with about 35 patients with candidemia in a year, our patient cohorts are rather small. Therefore, comparison of pre-intervention and intervention groups may be affected.

In conclusion, an individualized, thorough, and timely routine ID bedside service in terms of AFS consultation improves the application of clinical guidelines in the management of patients with *Candida* fungemia, especially guideline-oriented diagnostics and therapy. Even if our study lacks evidence on AFS improving mortality and prognosis of patients with candidemia, it is an essential part of ABS and should remain so. The presence and availability of AFS members at the ward might influence i.) the performance of diagnostic procedures such as BC collection and ii.) the prescribing behavior of clinicians for antimicrobials in general. Improvement of prescribing quality of antimicrobials may slow down development of resistance, may lead to better adherence to treatment guidelines for infectious diseases, and may finally affect their management and prognosis. Therefore, AFS should be highly encouraged.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request to the corresponding author.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.03.054.

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