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ORIGINAL PAPER

Appropriate use of antifungals: impact of an antifungal stewardship program on the clinical outcome of candidaemia in a French University Hospital

H. Benoist[1] · S. Rodier[1] · A. de La Blanchardière[2] · J. Bonhomme[3] · H. Cormier[2] · P. Thibon[4] · Guillaume Saint-Lorant[1]

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Abstract

Objectives The objective of this study was to compare clinical outcomes of patients with candidaemia before and after implementation of an antifungal stewardship program (AFSP).

Methods This study included all consecutive cases of candidaemia identified from January 2012 to December 2015 in a French University Hospital. Data were collected retrospectively for a period of 2 years before implementation of the AFSP, and prospectively for 2 years after. All cases were reviewed by a multidisciplinary panel of experts including infectiologists, a microbiologist and pharmacists to have a complete follow-up of patients.

Results 33 and 37 patients were finally included in the first and second period, respectively. The sites of entry of the candidaemia cases studied were as follows: intraabdominal in 29 cases (41.4%), central venous catheter 21 (30.0%), other or unknown: 20 (28.6%). Infectiologist consultations increased from 36.4 to 86.5% between the two periods with a significative impact on daily blood cultures which were more frequently performed in the second period ($p=0.04$), and the use of echinocandins which was more frequent in the second period (97.1% of cases vs 78.8%, $p=0.03$). The 3-month mortality rate declined from 36.4% in the first period to 27.0% in the second period ($p=0.4$).

Conclusions Despite the insufficient number of candidaemia cases and the presence of other unmodifiable risk factors of mortality which did not allow us to show a significant effect on the 3-month mortality, AFSP had a significant effect on daily blood cultures and echinocandin use as first-line therapy.

Keywords Candidaemia · Prescribing practice · Antifungal stewardship · Fungal infections

Introduction

Candida spp. was shown to be the fourth cause of nosocomial bloodstream infections (9%) in a 7.5-year American nationwide surveillance study, after coagulase-negative Staphylococci (31% of isolates), *Staphylococcus aureus* (20%), and *S. enterococci* (9%) [1]. In the past 20 years, incidence of candidaemia has increased steadily in many countries worldwide, [2] in particular in France where it concerned about 2600 patients in 2010 [3]. Candidaemia/invasive candidiasis (C/IC) is becoming an emerging problem in hospital practice due to an increased prevalence of susceptible hosts, i.e. patients with central venous catheters and/or immunosuppressive therapies added to a broad-spectrum antibiotic therapy [4].

C/IC is often fatal with a crude mortality rate of 46–75% of cases and a very variable attributable mortality of 5–71%,

✉ Guillaume Saint-Lorant
saintlorant-g@chu-caen.fr

1 Service de pharmacie, Pharmacie centrale, Centre Hospitalier Universitaire de Caen, avenue Côte de Nacre, 14033 Caen Cedex 9, France

2 Service des maladies infectieuses, Centre Hospitalier Universitaire de Caen, Caen Cedex 9, France

3 Service de microbiologie, Centre Hospitalier Universitaire de Caen, Caen Cedex 9, France

4 CPias Normandie, Centre Hospitalier Universitaire de Caen, Caen Cedex 9, France

unchanged for the last 2 decades [5, 6]. Furthermore, they extend the length of hospital stay and increase healthcare costs for patients who survive [5, 6]. Such mortality may be due to an absence or a delay in initial empirical therapy > 12H after the first positive blood sample for culture, and an inadequate choice, dosage or duration of prescription of the antifungal molecule [6, 7]. Removal of catheter(s), combined with an initiation of antifungal treatment within the first 48 h was independently associated with a decreased risk for both early and late mortality [8, 9].

As a result, implementation of antifungal stewardship program (AFSP) is strongly encouraged [10], on the basis of the effectiveness of antimicrobial stewardship on antibiotic prescriptions [11–13].

The objective of this study was to compare clinical outcomes of patients with C/IC before and after implementation of an antifungal stewardship program, over a large period of 4 years in a French University Hospital.

Patients and methods

Data collection

Our study included all consecutive adult and paediatric cases of candidaemia, identified by the microbiology laboratory from January 2012 to December 2015 in a 1407-bed University Hospital. Inclusion criteria were: (a) isolation of *Candida* spp. in one or more blood cultures and (b) the patient was still present and alive 48 h after the first blood culture. Thus, patients were excluded if they died or were transferred before the treatment was started. Data were collected retrospectively for a period of 2 years and 3 months (pre-intervention period: January 2012–March 2014) before implementation of the AFSP, and prospectively (post-intervention period: April 2014–December 2015) for 2 years after.

We collected information on: (a) demographic characteristics: age, sex; (b) chronic comorbidities and Charlson comorbidity index; (c) acute comorbidities including severe undernutrition; (d) therapeutic predisposing factors; (e) site of entry (catheter-related candidaemia was defined by clinical sepsis, the use of a central venous catheter and the presence of an identical species in culture from blood and the catheter tip, in the absence of another likely source of infection), *Candida* species and susceptibility to antifungal agents; (f) therapeutic management and outcomes. Data were collected from the laboratory information system (TDNexLabs, Technidata, France) and clinical data from paper or electronic medical records (Usv2-Crossway, Mckesson,USA).

In the antifungal stewardship program, the microbiologist first warns the infectiologist of the first positive cultures to *Candida* spp., the infectiologist then gives a recommendation in the unit based on ESCMID guideline for the diagnosis and management of Candida disease 2012: non-neutropenic and adult patients and send a patient follow-up to the pharmacist who will collect data. In the unit, the infectiologist reminds the first-prescriber of candidaemia management [14]. In case of candidaemia, (corresponding to at least one positive blood culture), CVC removal must be performed and a treatment with Mycafungin initiated. Afterwards, a fundus of the eye looking for chorioretinitis and a TTE had to be prescribed. Then two options are considered. One, in the absence of chorioretinitis and/ or endocarditis: either prescription of micafungin at the dose of 100 mg/day for patients weighing more than 40 kg and at the dose of 2 mg/kg/day for patients under 40 kg, or de-escalation towards fluconazole (IV or oral) according to antifungal resistance testing. Two, in case of chorioretinitis and/ or endocarditis, amphotericin B IV (1 mg/kg/day) with flucytosin (25 mg/kg/6 h) had to be prescribed. In case of renal failure, amphotericin B was replaced by liposomal amphotericin B (3 mg/kg/day). The duration of treatment has to be more than 14 days including 7 days after 2 successive negative blood cultures and clinical signs resolution. All cases were reviewed by a multidisciplinary panel of experts including an infectiologist, a microbiologist and a pharmacist to have a complete overview of patient records in each area of expertise, to determine the site of entry of the candidaemia and assess appropriateness of care, based on the following criteria: delay between microbiological results and treatment; adaptation to weight and renal function; adapted treatment duration; CVC removal; paraclinical examinations performed [daily blood culture until negative, fundus of the eye looking for chorioretinitis, trans-thoracic echocardiography looking for endocarditis, abdominal CT, and upper limb Doppler (for patients with CVC)].

Data were also collected for six outcomes: relapse, duration of stay, secondary location infection, and mortality at day 7, day 30 and 90.

Microbiological method

Blood culture bottles were incubated in Bact/Alert system (bioMérieux, France). In case of positive blood cultures, subcultures were performed on Sabouraud agar medium (Oxoid) and/or chromogenic medium (CAN2 ChromID Candida, bioMérieux, France). Species identification was performed using mass spectrometer Maldi Tof (Microflex LH/SH analyser, Bruker, USA). Minimum Inhibitory Concentrations (MICs) were obtained with Etest (BioMérieux, France) following the manufacturer's instructions.

Statistical analysis

Categorical variables were expressed as a number and percentage and compared with the Chi-squared test or the Fisher's exact test, depending on the expected values. Continuous variables were expressed as the median and interquartile range (IQR, 25th–75th percentiles) and were compared using the Kruskal–Wallis non parametric test. All statistical tests were two-tailed and a p-value of less than 0.05 was considered statistically significant. All statistical procedures were performed using the SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics (Table 1)

During the study period, 93 adult patients had at least one positive *Candida* blood culture and no paediatric cases were collected. Among them, after exclusion of 21 who died and 2 who were transferred within 48 h after the first blood culture, 70 patients were finally included.

Overall, no difference was observed before and after implementation of the AFSP, except for ICU admission, more frequent in the first period (54.6% vs 27.0%, $p=0.02$). Overall, patients were more often male (sex ratio M/F of 2.5) with a median age of 65.5 years (IQR 52–78). The most frequent comorbidities were malignancy and renal failure, observed in, respectively, 36 (51.4%) and 21 (30.0%) of cases. Sixty-one patients (87.1%) had a central venous catheter and 18 (25.7%) had abdominal surgery. Fifty-three

Table 1 Demographic characteristics, predisposing factors, and site of entry of candidemia before and after AFSP

Variable	Pre-intervention period ($N=33$)	Intervention period ($N=37$)	p-Value
Demographic characteristics			
Sex, male, *n* (%)	24 (72.7)	26 (70.3)	0.82
Age, years, median (IQR)	63 (47–78)	66 (54–77)	0.47
Chronic comorbidity, *n* (%)			
Malignancy	15 (45.5)	21 (56.8)	0.34
Renal failure	10 (30.3)	11 (29.7)	0.96
Diabetes	5 (15.2)	6 (16.2)	0.90
Heart failure	7 (21.2)	3 (8.1)	0.17
Liver failure	3 (9.1)	0	0.10
Respiratory failure	0	2 (5.4)	0.49
Organ or stem cell transplantation	3 (9.1)	2 (5.4)	0.66
Charlson comorbidity index, median (IQR)	2 (1–5)	2 (1–4)	0.99
Acute comorbidity, *n* (%)			
Neutropenia	0	3 (8.1)	0.24
Severe undernutrition	6 (18.2)	6 (16.2)	0.83
Concomitant bacterial infection	16 (55.2)	19 (51.4)	0.76
ICU admission before diagnosis	18 (54.6)	10 (27.0)	0.02
Predisposing therapeutic factors, *n* (%)			
Antibacterial exposure the previous 30 days	28 (84.9)	25 (67.6)	0.09
Antibiotic at the time of candidemia	25 (75.8)	23 (62.2)	0.22
Steroid or immunosuppressive therapy	5 (15.2)	9 (24.3)	0.34
Parenteral nutrition	4 (12.1)	10 (27.0)	0.12
Chemo/radiotherapy the previous 30 days	3 (9.1)	7 (18.9)	0.32
Central venous catheter	29 (87.9)	32 (86.5)	1
Abdominal surgery	8 (24.2)	10 (27.0)	0.79
Site of entry of candidemia, *n* (%)			0.07
Intraabdominal	9 (27.3)	20 (54.1)	
Central venous catheter	13 (39.4)	8 (21.6)	
Other or unknown	11 (33.3)	9 (24.3)	

patients (75.7%) had been exposed to an antibacterial within the previous 30 days. The sites of entry of the candidaemias were as follows: intraabdominal in 29 cases (41.4%), central venous catheter 21 (30.0%), other or unknown: 20 (28.6%). Candidaemia were classified as nosocomial in 52 cases (74.3%). The most common *Candida* species were *C. albicans* in 40 cases (57.1%; period 1: $n=24$, period 2: $n=16$), *C. glabrata* in 14 cases (20.0%; period 1: $n=5$, period 2: $n=9$) and *C. parapsilosis* in 6 cases (8.6%; period 1: $n=3$, period 2: $n=3$). Sensitivities tests were implemented only from period 2. No resistance for *C. albicans* and *C. parapsilosis* was found. A single strain was caspofungin-resistant in an intensive care unit patient. Caspofungin was stopped after a pluridisciplinary meeting where unanimous decision for withdrawal of care was taken.

Therapeutic management and outcomes (Table 2)

Infectiologist consultations increased from 36.4 to 86.5% between the 2 periods ($p<10^{-3}$) with a significant impact on daily blood cultures which were more frequently performed in the second period ($p=0.04$), and the use of echinocandins (caspofungin or micafungin) which was more frequent in the second period (97.1% of cases vs 78.8%, $p=0.03$). Global mortality rates at 7 days, 1 and 3 months were, respectively, 2.9%, 20.0% and 31.4%. The 3-month mortality declined from 36.4% in the first period to 27.0% in the second period, but this difference was not statistically significant ($p=0.40$).

Table 2 Therapeutic management and clinical outcomes before and after implementation of AFSP

Variable	Pre-intervention period ($N=33$)	Intervention period ($N=37$)	*p*-Value
Management of cases			
Infectiologist consultation, *n* (%)	12 (36.4)	32 (86.5)	$<10^{-3}$
CVC removal, *n* (%)	28/29 (96.6)	31/32 (96.9)	1
CVC removal ≤ 24 h, *n* (%)	24/29 (82.8%)	22/32 (68.8)	0.20
Daily blood culture (until negative), n (%) (MD: 2)	27 (87.1)	37 (100)	0.04
Transesophageal/trans-thoracic echocardiography, *n* (%) (MD: 1)	26 (81.3)	32 (86.5)	0.55
Eye funduscopic examination, n (%) (MD: 1)	12 (37.5)	22 (59.5)	0.07
Abdominal CT, *n* (%) (MD: 4)	14 (46.7)	21 (58.3)	0.34
Upper limb doppler (if CVC), *n* (%)	12/29 (41.4)	10/32 (31.2)	0.41
Antifungal treatment			
Delay between microbiological results and treatment			
≤ 48 h, *n* (%)	31 (93.9)	36 (97.3)	0.60
0 Day, *n* (%)	29 (87.9)	32 (86.5)	1
Drug used, *n* (%)[a]			$<10^{-3}$
Caspofungin	26 (78.8)	11 (32.4)	
Micafungin	0 (0)	22 (64.7)	
Fluconazole	7 (21.2)	1 (2.9)	
Loading dose (if applicable), *n* (%)	30/32 (93.8)	14/14 (100)	1
Adapted duration of treatment, *n* (%)	32 (97.0)	37 (100)	0.47
Antifungal de-escalation, *n* (%) (MD: 4)	12 (40.0)	19 (52.8)	0.30
Outcomes			
Relapse (positive blood culture after discontinuation of treatment), *n* (%) (MD: 3)	2 (6.5)	1 (2.8)	0.59
Delay between treatment and patient discharge[b], days, median (IQR)	22 (15–29)	21 (13–40)	0.75
Secondary location infection, n (%) (MD: 1)	8 (25.0)	6 (16.2)	0.37
Mortality, *n* (%)			
≤ day 7	1 (3.0)	1 (2.7)	1
≤ day 30	7 (21.2)	7 (18.9)	0.81
≤ day 90	12 (36.4)	10 (27.0)	0.40

MD missing data, *CVC* central venous catheter, *IQR* interquartile range

[a]Initiation of treatment, three dual antifungal therapies excluded

[b]22 deceased patients excluded

Discussion

Because candidaemia is an infection with a high mortality rate, it is essential to identify risk factors for attributable mortality and to set up a stewardship program to optimize infection management. This study was carried out over a large period (4 years), which made it possible to include 70 patients. The main causes of candidaemia remain classical infection of CVC and intraabdominal infection. Analysis of crude mortality 90 days after first positive blood sample has shown that 21 patients died before treatment initiation and 22 despite the treatment. Studies have shown that delay in administration of antifungal therapy is an independent predictor of hospital mortality, if the appropriate antifungal therapy is not administered within 12 h, 24 h or 48 h after the first positive blood sample [7, 9]. AFSP has allowed 86.5% of candidaemia to be monitored by an infectiologist. Our study shows a significant effect on frequency of daily blood cultures and on use of an echinocandin as first-line antifungal therapy, and a trend towards more frequent eye funduscopic examinations (screening for chorioretinitis). Setting up a multidisciplinary program has already demonstrated a decrease in inappropriate antifungal prescription for candidaemia [15–19]. Nevertheless, no effect on 3-month mortality was observed. This lack of significant progress on attributable mortality may be explained by the fact that modifiable risk factors of mortality attributable to candidaemia (such as removal of the CVC, delay between detection of candidaemia and antifungal therapy, treatment duration) were already well taken care of before implementation of AFSP, especially because a larger cohort of patients was treated in the intensive care unit.

The strengths and limitations of this study are its duration as well as the review of each patient file by a multidisciplinary team. The series included is significant, but headcounts are too low to have a sufficient statistical power to demonstrate an impact on outcomes, especially mortality. Moreover, the practices were not entirely bad in the pre-intervention period where the infectiologist was consulted (36.4%) and training efforts of prescribers had been made. However, more patients were taken care of in the ICU where practices are possibly better. Thus, the impact of AFSP on overall candidaemia mortality has not yet been demonstrated, and there is still no evidence of impact of AFSP on patient outcomes [15, 20, 21]. These efforts must be maintained. Multi-centre studies with larger populations are urgently needed to demonstrate a significant impact of AFSP on candidaemia mortality.

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