Invasive *Candida* infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006–2008)

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Abstract

A prospective, observational, multicentre study of invasive candidosis (IC) in surgical patients in intensive care units (ICUs) was conducted from 2006 to 2008 in 72 ICUs in 14 European countries. A total of 779 patients (62.5% males, median age 63 years) with IC were included. The median rate of candidaemia was 9 per 1000 admissions. In 10.8% the infection was already present at the time of admission to ICU. *Candida albicans* accounted for 54% of the isolates, followed by *Candida parapsilosis* 18.5%, *Candida glabrata* 13.8%, *Candida tropicalis* 6%, *Candida krusei* 2.5%, and other species 5.3%. Infections due to *C. krusei* (57.9%) and *C. glabrata* (43.6%) had the highest crude mortality rate. The most common preceding surgery was abdominal (51.5%), followed by thoracic (20%) and neurosurgery (8.2%). *Candida glabrata* was more often isolated after abdominal surgery in patients ≥60 years, and *C. parapsilosis* was more often isolated in neurosurgery and multiple trauma patients as well as children ≤1 year of age. The most common first-line treatment was fluconazole (60%), followed by caspofungin (18.7%), liposomal amphotericin B (13%), voriconazole (4.8%) and other drugs (3.5%). Mortality in surgical patients with IC in ICU was 38.8%. Multivariate analysis showed that factors independently associated with mortality were: patient age ≥60 years (hazard ratio (HR) 1.9, p 0.001), central venous catheter (HR 1.8, p 0.05), corticosteroids (HR 1.5, p 0.03), not receiving systemic antifungal treatment for IC (HR 2.8, p <0.0001), and not removing intravascular lines (HR 1.6, p 0.02).

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Introduction

Invasive candidosis (IC) has a significant impact on morbidity, mortality, length of hospital stay, and healthcare costs in critically ill patients [1]. The overall mortality for these patients is high. Candidaemia increases mortality rates in the range of 20−49% [2] and the attributable mortality has been calculated to be around 15% [3].

A nationwide US surveillance study demonstrated that the crude mortality rate of IC was 47% for patients in intensive care units (ICUs) and 29% for patients in a hospital ward [4]. In a multicentre study of ICUs in France from 2005 to 2006, the mortality associated with IC in ICUs was also high (45.9%) [5].

In a previous European Confederation of Medical Mycology (ECMM) prospective multinational study performed in seven European countries, the rates of candidaemia ranged from 0.20 to 0.38 per 1000 hospital admissions [6]. Intensive care treatments accounted for about 40% of all episodes of candidaemia in various surveys conducted in Europe [2,6,7]. Moreover, two recent European studies documented the significance of fungal diseases in the intensive care setting [8,9].

Although *Candida albicans* is still the main cause of IC, a shift towards non-*albicans* species in some patients and age groups has been observed over the past two decades [10,11]. Numerous large surveillance studies have provided important information regarding the epidemiology of candidaemia. However, information in particular on surgical patients in ICU remains scarce. Therefore, the ECMM initiated a prospective multicentre survey on IC in surgical patients in ICU.

The aims of the survey were to expand our knowledge of the characteristics of surgical patients with IC in ICU to understand the epidemiology of IC and to determine which factors are associated with mortality.

Methods

Study design and patients

ECMM survey in surgical patients in ICU with invasive candidosis was a prospective, multicentre, observational laboratory-based study. Patient recruitment began in 2006 (in France and Turkey, 2007) and concluded on 31 December 2008 (Table 1).

Fourteen countries participated. Each country had a national coordinator who collaborated with colleagues in ICU. Surgical ICU patients with IC were eligible for enrolment. In each case, a standardized questionnaire was filled out by clinicians and by microbiologists in the mycology laboratories. Each patient was assigned a code number by the national coordinator (the

TABLE 1. European Confederation of Medical Mycology prospective study of *Candida* infections in 779 surgical patients in ICU from 14 countries

Country	Cases	(%)	Country	Cases	(%)
Austria	97	12.5	Italy	216	27.7
Czech Republic	77	9.9	the Netherlands	18	2.3
Finland	10	1.3	Portugal	6	0.8
France	55	7.1	Spain	96	12.3
Germany	13	1.7	Sweden	101	13.0
Greece	41	5.3	Turkey	11	0.4
Hungary	5	0.6	UK	33	4.2

patient's name and birth were removed) before sending the questionnaire to the coordinator for the whole study. Local ethical committee approval at each participating centre was expedited but no approval was required owing to the purely observational nature of the study.

The aim was to include 50−75 patients per country to be able to include at least 800 patients.

Inclusion criteria

All surgical patients in ICU who had a microbiologically documented IC were included in the study, and data were recorded regardless of whether they had IC at admission or developed it during their stay in ICU.

Clinical data

Invasive candidosis with or without candidaemia were defined by a culture positive for *Candida* obtained from blood or other normally sterile body sites, according to the EORTC/MSG criteria [12]. The infections were considered ICU-acquired when diagnosed ≥48 hours after admission to ICU.

Collected data included demographic characteristics; type of preceding surgery; risk factors and underlying diseases; diagnosis of fungal infection; index of severity of illness at admission to ICU (APACHE II score); antifungal prophylaxis and treatment; and outcome at day 30 after diagnosis of *Candida* infection (Table 2).

Data on removal of central venous catheters (CVCs) was collected and culture results were documented. Patient outcome at day 30 after detection of IC, time in ICU, and time of hospital discharge were determined. Epidemiological data concerning the ICU were collected, including number of admissions and patient days.

Prophylactic antifungal therapy was defined as the administration of an antifungal drug to a patient at high risk for *Candida* infection but with no symptoms, signs, or laboratory confirmation of such infection. First-line therapy was defined as the first antifungal drug given to the patient either as empirical therapy or as therapy after a *Candida*-positive culture from a sterile body site.

TABLE 2. Demographic data and clinical characteristics of 779 surgical patients in ICU with invasive candidosis

Variable	Median:mean (range), or n/x (%)
Age (years)	63:58.7 (0–91)
Gender (male)	487 (62.5)
Days of hospitalization before admission to ICU	2:15.2 (0–744)
IC present at admission to ICU	84/719 (10.8)
Days in ICU before IC	12:17.9 (0–190)
Rate of candidaemia per 1000 admissions to ICU	9:12 (3–28)
Total days in ICU	23:33 (0–329)
Candida colonization (within 2 weeks before IC)	234/400 (58.5)
Antifungal prophylaxis (within 2 weeks before IC)	129 (16.5)
Antifungal treatment	670/720 (93)
Type of preceding surgery	
Abdominal	401 (51.5)
Thoracic	156 (20.0)
Vascular	49 (6.3)
Neurosurgery	64 (8.2)
Orthopaedic	12 (1.5)
Multiple trauma	54 (6.9)
Solid organ transplant	26 (3.3)
Other	17 (2.2)
Repeated surgery	166/752 (21.3)
Clinical characteristics[a]	
Pancreatitis	7 (0.9)
Solid tumour	178 (22.9)
Burns	9 (1.2)
Diabetes mellitus	118 (15.2)
Human immunodeficiency virus infection	0
Haematological malignancy	26 (3.3)
Rheumatological disease	23 (3)
Broad-spectrum antibiotics in the last 2 weeks	511 (78.4)
Steroid use in the last 2 weeks	176 (22.6)
Total parenteral nutrition	346 (44.4)
Dialysis at presentation	142 (18.2)
Invasive mechanical ventilation	468 (60)
Central venous catheter	776 (96.6)
Prosthetic devices	43 (5.5)
Outcome	
Death	296/763 (38.8)

Abbreviations: IC, invasive candidosis; ICU; intensive care unit.
[a]More than one factor may be present in a single case.

Mycological data

Microbiological data, such as date and number of positive blood cultures, blood culture system used, culture of intravascular lines, presence of mucous membrane colonization, and yeast species isolated were collected for each patient.

Identification of *Candida* isolates at species level was performed in the microbiology laboratories of each institution using standard methods.

Statistical analysis

Statistical analyses consisted of descriptive frequency tables and Pearson's chi-square or Fisher's exact test for clinical and mycological characteristics. Statistical significance was assumed for a two-tailed p-value <0.05. Median and range were calculated as continuous variables. Incidence per 1000 admissions to ICU was also calculated.

Multivariate survival analysis

To determine which factors were associated with mortality in patients with IC, several approaches of multivariate survival analysis using a proportional hazards method proposed by Cox were conducted. The first approach was to fit the model with all patients in the data set to study overall survival. The second approach was to fit the same model with the patients infected by a specific *Candida* species, for each species documented. Survival time up to 30 days from the date of first positive diagnosis of IC was calculated for each patient. All models started by including a set of risk factors, underlying diseases, type of preceding surgery, and background information as covariates. Variables with the least influence on survival (p-value >0.15) were excluded from the model one by one. Estimates from the models were obtained as hazard ratios and the associated 95% confidence intervals. All statistical analyses were conducted using SAS 9.3 software and R version 2.10.1.

Results

Patient characteristics and episodes of infection

A total of 72 ICUs in 14 countries participated. A total of 807 patients were recruited, 28 of whom were subsequently excluded from analysis because they did not fulfil the inclusion criteria of having IC.

Of the 779 eligible patients included in the study, 42 were <18 years old. The median duration of hospital stay before admission to ICU was 2 days (mean 15.2 days, range 0–744). Infection was present before admission to ICU in 84 (10.8%) of the patients and occurred ≤48 hours after admission to ICU in another 68 (8.7%) of the patients; it was considered ICU-acquired (occurred ≥48 hours after ICU admission) in 627 (80.5%) of surgical patients. The total duration of stay in ICU was median 23 days (mean 33 days, range 0–329 days). The shortest stay was associated with *Candida glabrata* (median 18 days) and the longest with *Candida parapsilosis* (median 30 days).

Fifty-seven ICUs in nine countries reported all episodes and could provide the total number of surgical admissions. Their median rate of candidaemia was 9 (range 3–28) per 1000 surgical admissions to ICU.

Localization of invasive infection was as follows: 637 patients (81.8%) with isolated candidaemia; 126 (16.2%) with candidaemia and with deep infection (*Candida* was isolated using sterile technique from peritoneal fluid in 46 patients, abdominal abscess in 42 patients, pleural fluid in eight patients, various biopsies in seven patients, deep surgical wounds in six patients, cerebrospinal fluid in four patients, bile in three patients, and various other normally sterile body fluids in ten patients) and 16 patients (2%) with IC but without documented candidaemia.

In the latter 16 patients, a positive culture was obtained by sterile means from the peritoneal fluid, oesophagus biopsy, pleura, deep abdominal wound, abdominal abscess, and mediastinum.

TABLE 3. Species distribution of 807 *Candida* isolates in 779 patients

Candida species	Number of isolates	(%)
C. albicans	436	54.0
C. parapsilosis	149	18.5
C. glabrata	111	13.8
C. tropicalis	49	6.0
C. krusei	20	2.5
C. lusitaniae	14	1.7
C. dubliniensis	9	1.2
C. guillermondii	5	0.6
C. ciferrii	4	0.4
Other[a]	9	1.2
Total	807	100

[a]*C. pelliculosa*, n = 3; *C. haemoloni*, n = 2; *C. kefyr*, n = 2; *C. lambica*, n = 1; *C. humicola*, n = 1.

Among the 763 patients with candidaemia, the time from ICU admission to first positive blood culture drawn was ≤5 days for 127 patients (22%). The time from ICU admission to first positive blood culture was a median of 12 days (mean 17.9 days, range 0–190), with medians of 6 days for *Candida krusei*, 7 days for *C. glabrata*, 10 days for *C. albicans* and *Candida tropicalis*, and 16 days for *C. parapsilosis*.

Concomitant bacteraemia was observed in 34 of 763 patients (4.9%) with candidaemia.

Of the affected patients, 62.5% were male and 37.5% were female. The median age was 63 years (mean age 59 years, range 3 days to 91 years). Among the 779 surgical patients, 401 had undergone abdominal surgery, 156 thoracic surgery, 49 vascular surgery, 64 neurosurgery, 54 multiple trauma, 26 solid organ transplant (13 liver, six heart, three kidney, two lung, one heart and liver, and one spleen and liver), and 29 other surgery.

Repeated surgical intervention was necessary in 166 patients (21.3%) during their stay in ICU, mainly after previous abdominal surgery (60%).

For the main clinical characteristics of the patients, see Table 2.

Mycology data

In the 779 patients with IC a total of 807 isolates were identified. *Candida albicans* was isolated in 54% of cases, followed by *C. parapsilosis* in 18.5%, *C. glabrata* in 13.8%, *C. tropicalis* in 6%, *C. krusei* in 2.5%, and other species in 5.3%, see Table 3. If Spain and Italy are excluded, *C. glabrata* ranks second most common. Two or three different *Candida* species were found in 24 and two patients, respectively.

Candida colonization cultures were taken in 51% of patients. In 58.5% of them a *Candida* species was isolated, and the same colonizing species was the cause of IC in 94.5% of these cases.

Candida parapsilosis was isolated more often in thoracic, neurosurgical, solid organ transplant and multiple trauma patients compared with abdominal surgery patients. Abdominal surgery patients had the highest rate of *C. glabrata* infections (16.2%) compared with the other patient groups, and neurosurgical patients had the lowest rate (1.5%) (Fig. 1).

Of the 42 patients <18 years, 26 were children ≤1 year old. The species distribution was *C. albicans* in 42.3% (n = 11), *C. parapsilosis* in 38.5% (n = 10), *C. glabrata* in 7.7% (n = 2), *C. tropicalis* in 7.7% (n = 2) and *Candida guilliermondii* in 3.8% (n = 1).

The prevalence of *C. glabrata* increased with patient age; 71.8% of the cases occurred in patients aged ≥60 years.
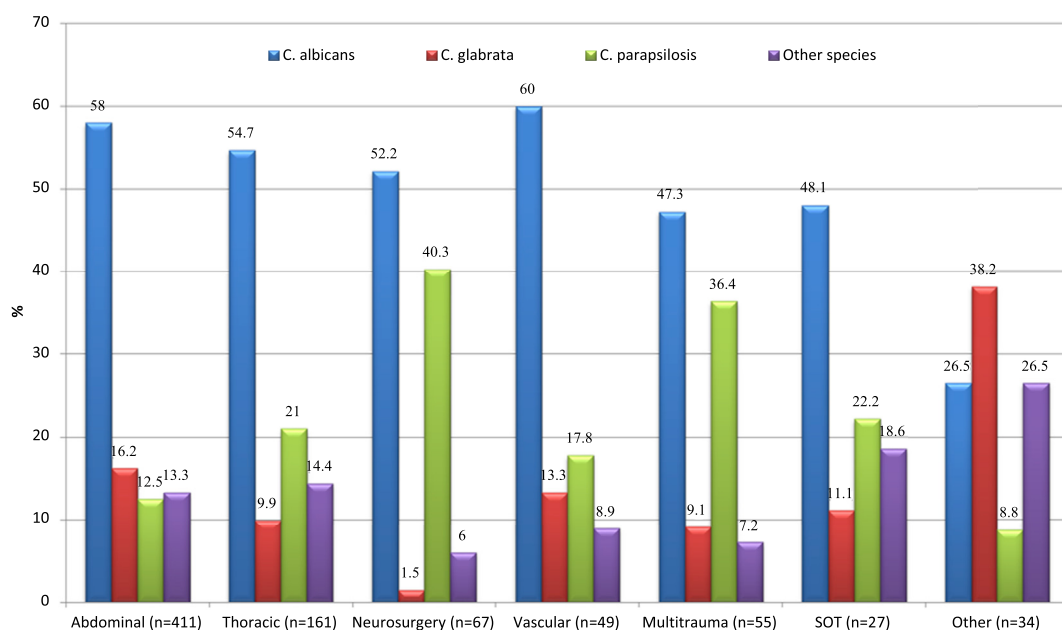
FIG. 1. *Candida* species (*n* = 807) distribution in 779 surgical patients in intensive care units.

Antifungal prophylaxis

A total of 129 patients were receiving systemic antifungal prophylaxis (16.5%) and developed a *Candida* infection. Patients received fluconazole (78%), caspofungin (7.1%), voriconazole (3.2%), liposomal amphotericin B (5.6%), amphotericin B deoxycholate (3.9%), or other drugs (2.2%). For three patients the name of the drug was not recorded. Of the 98 patients who received fluconazole as prophylaxis, *C. albicans* was the cause of IC in 44%, followed by *C. parapsilosis* in 27.6%. *Candida glabrata* and *C. krusei* were isolated in 17.4% and 4.1% of patients, respectively.

Initial antifungal treatment

For 670 patients, the initial systemic antifungal drug was recorded. Fifty patients received no treatment, and for 59 patients the data were not recorded.

Fluconazole, administered to 60% (402 of 670) of the patients, was the antifungal most frequently used to treat *Candida* infection, followed by caspofungin (125 patients, 18.7%), lipid-based amphotericin B (87 patients, 13%), voriconazole (32 patients, 4.8%), and various other drugs (24 patients, 3.5%).

Interventions associated with antifungal treatment

Survival with lines removed or not removed was recorded for 411 out of 779 patients. The vascular catheter was removed or changed upon diagnosis of candidaemia in 288 of 411 patients (70%). The survival rate was 68.1% for patients from whom the lines were removed, compared with 48.8% (p 0.02) in patient with lines not removed (Table 4).

Outcome

The overall crude mortality at day 30 was 38.8% (same in males and females). In the 11 infants 3–12 months old the mortality was 72.7%; if the four infants <3 months old are included, the mortality was 67%.

APACHE II scores were recorded for 197 patients. APACHE II score >20 was recorded for 100 patients and 49 (49%) of these patients died. Of the 97 patients with APACHE II score ≤20, 15 (15.5%) died.

Infections caused by *C. krusei* and *C. glabrata* had the highest crude mortality rates (57.9% and 43.6%, respectively) compared with *C. tropicalis* (26.8%), *C. albicans* (36.8%), and *C. parapsilosis* (36.2%).

Multivariate survival analysis of factors associated with death for various infections

Table 4 shows the results of multivariate analysis of factors associated with death in surgical patients with IC in ICU. In the first approach the model was applied to all patients and in the second the model was applied excluding information on catheter removal.

TABLE 4. Results from multivariate survival analysis of all patients with IC, in which records of line removed were included (number of patients included was 418) or were excluded (number of patients included was 719)

Risk factor	No. of deaths	No. of survivals	Hazard ratio	95% hazard ratio confidence limits	p-value
Records of line removed included (*n* = 418)					
Age					
Older than 60 years	97	150	1.91	1.30–2.80	0.001
60 years and younger	37	134	1.00		
Type of infection					
ICU-acquired infection	125	241	1.72	0.87–3.40	0.12
Infection prior to ICU admission	9	43	1.00		
Treatment					
No	23	15	2.80	1.74–4.50	< 0.0001
Yes	111	269	1.00		
Line removed					
No	53	70	1.55	1.08–2.23	0.02
Yes	81	214	1.00		
Corticosteroid					
Yes	42	59	1.52	1.05–2.20	0.03
No	92	225	1.00		
Total parenteral nutrition					
Yes	83	150	1.34	0.94–1.90	0.11
No	51	134	1.00		
CVC					
Yes	122	229	1.84	1.01–3.34	0.05
No	12	55	1.00		
Prosthetic device					
Yes	16	16	1.64	0.96–2.80	0.07
No	118	268	1.00		
Records of line removed excluded (*n* = 719)					
Age					
Older than 60 years	166	258	1.98	1.48–2.66	< 0.0001
60 years and younger	62	233	1.00		
Type of infection					
ICU-acquired infection	209	390	2.10	1.31–3.37	0.002
Infection prior to ICU admission	19	101	1.00		
Treatment					
No	39	31	2.91	2.06–4.12	< 0.0001
Yes	189	460	1.00		
Corticosteroid					
Yes	68	97	1.42	1.07–1.89	0.02
No	160	394	1.00		
Total parenteral nutrition					
Yes	122	207	1.38	1.06–1.80	0.02
No	106	284	1.00		
CVC					
Yes	198	373	1.47	0.99–2.18	0.05
No	30	118	1.00		
Prosthetic device					
Yes	19	21	1.51	0.94–2.43	0.09
No	209	470	1.00		

Abbreviations: CVC, central venous catheter; ICU, intensive care unit.

Candida albicans infection

When analysis excluded data records of whether lines were removed or not, the results were almost the same except that patients without treatment were at much higher risk (hazard ratio 3.2, p <0.0001) and CVC was no longer a statistically significant factor at the 5% level (Table 5). One major difference was that patients with repeated surgery had a lower risk of dying (hazard ratio 0.6, p 0.01).

TABLE 5. Results from multivariate survival analysis of patients infected by *Candida albicans*, *Candida glabrata* and *Candida parapsilopsis* where records of line removed were included

Risk factor	No. of deaths	No. of survivors	Hazard ratio	95% hazard ratio confidence limits	p-value
Results for *C. albicans* (number of patients included was 230)					
Age					
Older than 60 years	54	82	1.84	1.12–3.02	0.02
60 years and younger	23	71	1.00		
Type of infection					
ICU-acquired infection	73	126	2.98	1.08–8.21	0.04
Infection prior to ICU	4	27	1.00		
Treatment					
No	12	10	2.14	1.12–4.07	0.02
Yes	65	143	1.00		
Line removed					
No	33	42	1.72	1.08–2.73	0.02
Yes	44	111	1.00		
Repeated surgical					
Yes	12	45	0.43	0.23–0.81	0.01
No	65	108	1.00		
Corticosteroid					
Yes	27	32	1.88	1.17–3.02	0.01
No	50	121	1.00		
CVC					
Yes	70	118	2.63	1.20–5.75	0.01
No	7	35	1.00		
Results for *C. glabrata* (number of patients included was 95)					
Age					
Older than 60 years	28	37	2.25	0.91–5.56	0.08
60 years and younger	6	24	1.00		
Treatment					
No	8	3	5.75	2.35–14.04	0.0001
Yes	26	58	1.00		
Total parenteral nutrition					
Yes	19	22	2.67	1.28–5.55	0.01
No	15	39	1.00		
Results for *C. parapsilosis* (number of patients included was 131)					
Age					
Older than 60 years	26	36	1.90	0.99–3.66	0.05
60 years and younger	14	55	1.00		
Treatment					
No	8	7	2.89	2.89–6.31	0.01
Yes	32	84	1.00		

Abbreviations: CVC, central venous catheter; ICU, intensive care unit.

Candida glabrata and *C. parapsilosis* infection

The results shown in Table 5 are from the model that included all patients infected by *C. glabrata* and *C. parapsilosis*. Information about patients' catheters was excluded because it did not have any influence on survival.

Discussion

This ECMM study is to our knowledge one of the few large prospective studies on IC carried out exclusively on surgical patients in ICUs.

The median rate of candidaemia, calculated for 57 ICUs from nine countries, was 9 per 1000 surgical admissions to ICU, consistent with the Bougnoux prospective multicentre study of surgical patients in ICU with candidaemia [13]. However, our range (3–28) was wide. Finland had the lowest rate, while Italy and Spain had the highest. In recent point prevalence studies, a candidaemia incidence of 6.9 per 1000 ICU patients was reported [14]. However, that study also included both medical and surgical patients.

Candida albicans accounted for 54% of invasive isolates, followed by *C. parapsilosis* for 18.5%, *C. glabrata* for 13.8%, *C. tropicalis* for 6%, *C. krusei* for 2.5%, and other species 5.3%. Compared with other studies, a high incidence of *C. parapsilosis* was recorded—the incidence is usually around 7–13%. Concomitant bacteraemia was observed in 5% of cases, and in 3.7% more than one *Candida* species was isolated from blood. This is consistent with Jensen et al. [15], who recently reported that among 530 episodes of candidaemia, 2.8% had mixed candidaemia.

The species distribution in this study also showed geographic differences. *Candida albicans* was the most common *Candida* species. In southern Europe, *C. parapsilosis* ranked second and *C. glabrata* third in frequency, whereas in northern Europe, *C. glabrata* ranked second and *C. parapsilosis* third. These geographic differences have been described before [16,17].

The median duration of hospital stay before admission to ICU was short at 2 days, and the median total stay in ICU was 23 days. The majority (80.5%) of surgical patients developed an ICU-acquired infection ≥48 hours after ICU admission. Of this majority, 98% presented with candidaemia a median of 12 days after ICU admission.

However, time in ICU to first positive blood culture varied with the species, being shortest for *C. krusei* and *C. glabrata* (median 6 days and 7 days, respectively) and longest for *C. parapsilosis* (16 days), with *C. albicans* between (10 days). In only 22% of patients did candidaemia occur within 5 days after ICU admission. Although this percentage is lower than has been previously reported by ICUs [5], the fact that 22% of patients developed candidaemia < 5 days after ICU admission suggests that *Candida* species such as *C. glabrata* and *C. krusei* should be taken into account in empirical antimicrobial therapy, even in cases of sepsis occurring early during ICU stay.

The predominance of abdominal (51.5%) and thoracic (20%) pathologies underlying candidaemia, age ≥60 years, and males (62.5%) in our patient group is emphasized by the data in Table 5. Male gender seems to be a risk factor. This is consistent with other reports [16,17].

The incidence of *C. glabrata* infection was greater in patients after abdominal surgery (16.2%) compared with patients after thoracic surgery (9.9%), multiple trauma (8.8%) and neurosurgery (1.5%). Infection with *C. glabrata* was also associated with older age, which has been reported previously [16,17]. This might reflect the fact that colonization of the gastrointestinal tract with *C. glabrata* increases with older age [17,18]. Incidence of *C. parapsilosis* infection in patients after abdominal surgery was lower (12.4%) compared with neurosurgery (40.3%) and

multiple trauma (35.1%). *Candida parapsilosis* can be isolated from the patients' skin, the hands of healthcare workers, and the hospital environment and is associated with colonization of catheters.

This could explain the high rate in multiple trauma patients with broken skin barriers, but the high rate in neurosurgery patients has yet to be elucidated. One reason may be inadequate infection control measures in some ICUs. Furthermore, GISIA-3 data highlight an association between parenteral nutrition and *C. parapsilosis* [19]. Age also seems to determine predisposition to different *Candida* species. In children ≤1 year old *C. parapsilosis* was isolated in 38.5% of cases, while *C. glabrata* was rarely isolated. This finding is consistent with a recently published global study on neonates [20].

Patients with candidaemia frequently have a CVC in place, as was the case in 97% of the patients in this ECMM survey. Recent guidelines for the management of candidosis strongly recommend early CVC removal in all non-neutropenic patients with candidaemia [21,22] and in patients with CVC-related candidaemia [23].

In this ECMM study, CVC removal was significantly associated with survival compared with maintained CVC. The results of Leroy et al. and Tortorano et al. were similar (39.4% versus 60.9% and 39% versus 53%, respectively) [5,7]. Catheter removal has been associated with an improved probability of survival in other studies as well [24,25]. However, in our multivariate analysis CVC removal after candidaemia with *C. glabrata* and *C. parapsilosis* did not have a significant impact on survival, in contrast to *C. albicans* infections. Culture from the catheter tip was recorded in this study in only 284 (36.5%) cases. *Candida albicans* was the most common species (60.6%) isolated from the catheters, followed by *C. parapsilosis* (15.8%), *C. tropicalis* (12.8%), and *C. glabrata* (7.9%). In a recent scanning electron microscopy study [26] including 172 patients, yeasts were detected in significantly more catheters obtained from men than from women (p <0.01). This is inconsistent with the results of this ECMM study. The percentages of women and men with an infected catheter were almost the same, 58.8% and 58.1%, respectively. This variation between the two studies emphasizes the need for further investigation of the prevalence of *Candida* species biofilms in catheters.

According to several studies, only 5−15% of patients are colonized by *Candida* species at admission to ICU, but this progressively increases with time to 50−80% [27,28]. Growing evidence suggests that monitoring of *Candida* colonization in surgical patients and clinical prediction rules based on combined risk factors may be used to identify ICU patients at risk of IC [27,28]. In this ECMM study, monitoring of *Candida* colonization was recorded for only 51% of cases. Even so, in investigated patients, except for 4.3%, the colonizing species was the same species that later caused IC. In 1.2% the colonizing species together with another *Candida* species caused IC.

Eggimann et al. [29] conducted a randomized, placebo-controlled trial to study the efficacy of fluconazole prophylaxis among 49 high-risk surgical patients with recurrent gastrointestinal perforations or anastomotic leakages. They reported that patients who received fluconazole were less likely to have abdominal colonization or infection (peritonitis) with *Candida* species, but they were unable to assess whether the prophylaxis affected the risk of acquiring candidaemia because of the small number of patients enrolled. According to recent European guidelines prophylactic usage of fluconazole is recommended in patients with recent abdominal surgery and recurrent gastrointestinal perforations or anastomotic leakages [22]. However, local epidemiology with *C. glabrata* and *C. krusei* must be regarded.

In our study, a total of 129 patients (16.5%) receiving systemic antifungal prophylaxis developed IC. Fluconazole was given as prophylaxis in 98 patients. In 44% of the patients *C. albicans* was the cause of IC, followed by *C. parapsilosis* in 27.6%. Species with known intrinsic resistance to azoles were over-represented in the breakthrough cases compared with the whole population. *Candida glabrata* and *C. krusei* were isolated in 17.4% and 4.1%, respectively.

Candidaemia is associated with significant morbidity [10]. Delay of therapy for candidaemia beyond 12 hours after blood sampling has been associated with an increase in in-hospital mortality from <20% to 40% [30].

In this study 93% of the patients with IC received treatment. Our data shows that patients who did not receive systemic antifungal treatment for IC ran a significantly higher risk of dying (p <0.0001).

Recent data suggest that echinocandins should be used as the first choice because overall survival of patients with candidaemia is improved. The recommendation for fluconazole is recommended with marginal strength only, except for *C. parapsilosis* [22].

In this ECMM study focused on surgical patients in ICUs, mortality was a median of 38.8%. In a 2006−2008 Italian study and a 2009 French study the rate was 46% [5,7]. The highest mortality in our study was associated with *C. glabrata* (43.6%) and *C. krusei* (57.9%) infections, followed by *C. parapsilosis* (36.2%) and *C. albicans* (36.8%), and lowest with *C. tropicalis* (26.8%). This finding contrasts with other studies of cancer patients in which *C. tropicalis* is usually associated with the highest mortality and *C. parapsilosis* with the lowest overall mortality [31].

Compared with other studies [5,7], our findings have a lower case fatality ratio in patients specifically admitted to ICU.

Significantly, risk factors associated with mortality in patients infected by *Candida* were species-dependent. Multivariate

analyses of patients with invasive *C. albicans* infection also showed a higher risk of death if the infection was ICU-acquired (p 0.04) and if CVC was not removed (p 0.02). This was not the case for ICI with *C. glabrata* and *C. parapsilosis*. Patients receiving total parenteral nutrition and suffering from invasive *C. glabrata* infection had a higher risk of death (p 0.01), which was not the case with *C. albicans* and *C. parapsilosis*.

Reasons for these differences need to be explored.

Some limitations of this study must be stressed, in particular that some questionnaires were incomplete, so information on severity of IC and complications such as septic shock were not collected. Also, the mycological analyses of the *Candida* strains were not carried out in a single reference laboratory. Haemodialysis, which has been acknowledged as a predictor factor of mortality was not assessed in this study either, due to missing data.

This ECMM *Candida* study of surgical patients in ICU provides significant information on IC in European surgical ICUs. *Candida glabrata* was more often isolated after abdominal surgery in patients ≥60 years, and *C. parapsilosis* after neurosurgery, in patients with multiple trauma as well as in children ≤1 year of age. This is highly relevant to primary antifungal regimens, given the diverse susceptibility patterns of different *Candida* species. With *C. glabrata* having reduced susceptibility to fluconazole and *C. parapsilosis* having reduced susceptibility to the echinocandins, primary antifungal regimens should be adjusted to the local epidemiology. The findings in our study emphasize the importance of establishing continuous national surveillance programs in each country, as well as in different patient populations and age groups, so that we may obtain the background data needed to develop national recommendations. The physicians also need to seriously consider their antifungal choices on local epidemiology of fungal infections.

Transparency Declaration

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