ORIGINAL ARTICLE

Attributable mortality of candidemia at a German tertiary hospital from 1997 to 2001 before the introduction of echinocandins

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Abstract

Objectives: The relevance of candidemia has increased over the last decades due to higher incidence rates in an ageing society. Studies on amphotericin B and fluconazole have shown high attributable mortality rates of 38% and 49% in the United States. Incidence rates and locational factors might have an impact on the mortality rates at the University Hospital of Cologne (UHC), Germany.

Methods: We performed a matched case-control study including 57 patients with candidemia, hospitalised at the UHC between 1 July 1997 and 30 June 2001. Controls were matched by age, sex, admission date, treatment on intensive care unit (ICU), number of days at risk, underlying diseases, surgical procedures and the Charlson Comorbidity Index.

Results: The incidence of candidemia was 3.5 per 10 000 admissions. For cases and controls, we observed in-hospital-mortality rates of 33.3% and 11.8%, and a 30-day mortality of 23.5% and 7.8% respectively. The attributable mortality rate to candidemia was 21.5%, and at 30 days, it was 15.7%. Underlying conditions were more frequent in cases than in controls, especially central venous catheter (80% vs 33%, \( P < .001 \)), chronic cardiovascular disease (39.2% vs 25.5%, \( P = .138 \)), treatment on ICU (31.4% vs 13.7%, \( P = .033 \)) and chronic liver disease (21.6% vs 0%, \( P < .001 \)).

Conclusions: The attributable mortality of candidemia at the UHC between 1997 and 2001 was lower compared to studies performed in the United States with a similar design. Contributing factors might be lower incidence rates and less comorbidities in our study.

KEYWORDS
Candida, fluconazole, invasive candidiasis, liposomal amphotericin B, mortality
1 | INTRODUCTION

Candidemia often results in a prolonged hospital stay and high morbidity and mortality.\(^1\) Candida spp. are one of the most common causes of nosocomial bloodstream infections (BSI). A study performed in 2011 in Germany, including data from 586 intensive care units (ICUs), observed Candida albicans as the fourth leading pathogen of central venous catheter (CVC) associated BSI.\(^4\) In 2004, Candida spp. ranked seventh of the pathogens of nosocomial BSI in Switzerland.\(^5\) Studies performed in the United States (US) reported that Candida spp. are among the four most common pathogens causing nosocomial BSI.\(^6\)-\(^8\) Well-established risk factors for candidemia are prior and prolonged antibiotic treatment, parenteral nutrition, haemodialysis, presence of CVC, prolonged hospitalisation and abdominal surgery. Immuno compromised patients and patients on ICU are at high risk for candidemia.\(^7\)^{9,10}

In 1988, a monocentric, retrospective, case-control study performed in Virginia, US, by Wey et al observed an attributable mortality of candidemia of 38%.\(^3\) Gudlaugsson et al re-analysed the situation at the same institution from 1997 to 2001 addressing the question if new treatment strategies, the introduction of fluconazole as treatment of choice for candidemia\(^11\) and emergence of triazole-resistant species\(^12\) influence the attributable mortality. In this second study, an increase of the attributable mortality to 49% was reported.\(^2\) In 2020, a similar study was performed at the University Hospital of Cologne (UHC), Germany, analysing the attributable mortality of candidemia after the introduction of echinocandins. Cornely et al observed a significantly lower attributable mortality of 26%.\(^13\)

Until now, little data on epidemiology, risk factors and mortality rates of candidemia have been published in Germany at the turn of the millennium. To study medical progress and to analyse trends and developments, historical comparators are needed. We therefore performed a retrospective, matched case-control study analysing the attributable mortality of candidemia at the UHC from 1997 to 2001.

2 | PATIENTS AND METHODS

We performed a retrospective, monocentric, case-control study analysing all hospitalised patients with nosocomial candidemia at the UHC, between 1 July 1997 and 30 June 2001. The UHC is a tertiary care teaching hospital, which had an average annual number of 44 863 admissions during that period. Nosocomial candidemia was defined as at least one positive blood culture for any Candida species occurring >24 hours after admission. Control patients were matched to candidemia cases, which did not have a sign of invasive Candida infection.

To ascertain the best matching to a control patient, we used a stepwise procedure. In the first step, we used SAP databases (SAP Graphical User Interface (SAP GUI) 750 for Windows, SAP SE) to generate a list of possible control patients matched by age ±6 years (children: age ±1 year, sex, admission ±18 months, treatment on ICU ±14 days, days at risk and underlying disease. In a second step, we took surgical procedures and the Charlson Comorbidity Index (CCI) into consideration.\(^14\) During the matching process, YB and PK were blinded to the outcome of each matched patient chosen by the predefined algorithm.

For reasons of comparability, we defined the day of candidemia diagnosis as day d0. This was the day at which a preliminary identification of a yeast was communicated to the treating physician, which triggered antifungal therapy and further measures (eg removal of indwelling central lines). The timespan from the initial identification of a yeast in blood culture to the subsequent identification to species level was zero to five days. For controls, do was defined as the last day of the timespan t0 after admission, which was equivalent to the timespan t0 between admission and first positive blood culture of case patients. If no suitable control patient matched by days at risk could be identified, the patient with the longest time of hospitalisation was chosen. In those cases, do was defined as the last day of hospitalisation for non-survivors and patients lost to follow-up, whereas for survivors the definition of d0 did not differ from other control patients and occurred beyond the day of discharge.

For both case and control patients, epidemiologic and demographic characteristics were documented. We captured data of the underlying disease, Charlson Comorbidity Index, and risk factors for candidemia. ICU stay and indwelling CVC were only considered as a risk factor if they were present at least two days before d0. Both groups were compared by time of hospitalisation before and after d0, the latter, respectively, for survivors and non-survivors. We calculated Day 30 and in-hospital mortality and defined mortality attributable to candidemia as the difference between the in-hospital mortality of cases and controls. For candidemia cases, we captured Candida species distribution, microbiological findings, susceptibility testing, outcome by species and treatment strategies. The dosage of antifungal drugs was stratified according to the maintenance dose, which was administered for the majority of treatment days.

Adherence to guidelines of the Infectious Diseases Society of America (IDSA) published in 2000\(^15\) was analysed considering diagnostic procedures (initial blood culture, species identification, susceptibility testing, echocardiography and ophthalmoscopy), treatment strategies (treatment for 14 days after first negative follow-up blood culture, removal of central venous catheter) and follow-up blood cultures. If case patients were discharged with ongoing antifungal therapy, treatment duration was presumed to be at least for 14 days after first negative follow-up blood culture.

Data were accessed through microfilmed and paper health records and entered into the electronic case report form FungiScope\(^\circledast\) CandiReg accessible through www.clinicalsurveys.net.\(^15\) CandiReg is approved by the local Institutional Review Board and Ethics Committee of the University of Cologne (Identifier 17-485) and registered at www.clinicaltrials.gov (NCT03450005). All data collected were transferred to IBM SPSS statistics v27 (IBM Corp. Released 2020; IBM SPSS Statistics for Windows, Version 27.0) and
Categorical variables are presented with frequencies and percentages, while continuous variables with median and interquartile range (IQR). We performed chi-square test and Fisher's exact test for categorical and Mann-Whitney U test for continuous variables. A two-tailed $P$-value <.05 was considered as statistically significant.

### 3 | RESULTS

#### 3.1 | Incidence

During the observation period, 62 patients hospitalised at the UHC developed candidemia, resulting in an incidence of 3.5 per 10 000 admissions. For five patients, only incomplete data sets could be retrieved, so that they were excluded from the analysis. Hence, 57 patients were enrolled. For 51 candidemia patients, a suitable control patient was matched.
3.2 | Baseline characteristics

Characteristics serving as matching criteria such as sex, median age, CCI and major surgery were similar across both groups (P = n.s.; Table 1). In eight cases, no suitable control patient matched by days at risk was identified. In these cases, we matched the patient with the longest time of hospitalisation. Discrepancies were 4 days in four cases and 9, 12, 14 and 31 days in one case, each. Established risk factors for candidemia were more frequently observed in cases than in controls, especially chronic cardiovascular disease (39.2% vs 25.5%, \( P = .138 \)), chronic liver disease (21.6% vs 0%, \( P < .001 \)), chronic renal disease (5.9% vs 2%, \( P = .617 \)), diabetes mellitus (13.7% vs 5.9%, \( P = .318 \)) and obesity (5.9% vs 2%, \( P = .617 \)). Treatment on ICU at least 2 days before d0 and mechanical ventilation (MV) was observed more often in cases than in controls (ICU: 31.4% vs 13.7%, \( P = .318 \)) and obesity (5.9% vs 2%, \( P = .617 \)). Treatment duration on ICU likewise was longer for cases than for controls (median 23.5 days vs 15 days, \( P = .570 \)). CVCs present at least two days before d0 were observed in 80% of cases and 33% of controls (\( P < .001 \); Table 1).

3.3 | Duration of hospitalisation

Overall median time until discharge was longer for cases (17 [IQR 9-48]) than for controls (12 [IQR 1-22], \( P = .003 \)). Median time until discharge of surviving case and control patients was 23.5 (IQR 10.5-48) and 6 days (IQR 1-19.5, \( P > .001 \)) respectively. However, for the deceased, median time until discharge was shorter for cases than for controls with 13 (IQR 6.3-52, \( P = .319 \)) days and 23 (IQR 13.75-46.5) days respectively (Table 1).

3.4 | Species distribution and antifungal susceptibility

\( C \) \textit{albicans} was the most frequent species identified (37/57 patients, 65%), followed by \( C \) \textit{glabrata} and \( C \) \textit{tropicalis} in 7/57 patients (12%) and 5/57 patients (9%) respectively. \( C \) \textit{krusei}, \( C \) \textit{lusitaniae}, \( C \) \textit{parapsilosis} and \( C \) \textit{pseudotropicalis} were diagnosed in one patient (1.8%) each. Three patients (5%) with \( C \) \textit{albicans} infection had mixed infections with a second fungal pathogen (\( C \) \textit{krusei}, \( C \) \textit{guilliermondii} and \( C \) \textit{glabrata}) (Table 2).

Susceptibility results were available for only seven isolates at the time of hospitalisation. At a later stage, 55 isolates were retrospectively tested in 2007.\(^{16}\) All analysed \( C \) \textit{albicans} isolates (39) were susceptible to amphotericin B and fluconazole. All \( C \) \textit{glabrata} isolates (8) were susceptible to amphotericin B, but not susceptible to fluconazole (1 resistant, 7 intermediate). Five \( C \) \textit{tropicalis} isolates have been analysed, all of them were susceptible to Amphotericin B, four were susceptible to fluconazole and one showed an intermediate susceptibility to fluconazole. \( C \) \textit{krusei} (2 isolates) was susceptible to amphotericin B but resistant to fluconazole, and \( C \) \textit{parapsilosis} (1 isolate) was susceptible to both amphotericin B and fluconazole. Table 3 shows the baseline characteristics of candidemia patients stratified by the underlying species.

### Table 2  Species distribution

| Candida infections (n = 57) | Patients (n) | Survivors n (%) | Non-Survivors n (%) |
|----------------------------|--------------|-----------------|---------------------|
| \( C \) \textit{albicans}\(^{a}\) | 37           | 21 (57%)        | 16 (43%)            |
| \( C \) \textit{glabrata} | 7            | 7 (100%)        | 0 (0%)              |
| \( C \) \textit{tropicalis} | 5            | 2 (40%)         | 3 (60%)             |
| \( C \) \textit{krusei} | 1            | 1 (100%)        | 0 (0%)              |
| \( C \) \textit{lusitaniae} | 1            | 1 (100%)        | 0 (0%)              |
| \( C \) \textit{parapsilosis} | 1            | 1 (100%)        | 0 (0%)              |
| \( C \) \textit{pseudotropicalis} | 1          | 0 (0%)         | 1 (100%)            |
| \( C \) NOS\(^{b}\) | 4            | 2 (50%)         | 2 (50%)             |
| Total | 54           | 34 (63%)        | 20 (37%)            |

\(^{a}\)Three patients had a mixed infection of two \( C \) \textit{Candida} species: \( C \) \textit{albicans} + \( C \) \textit{glabrata}, \( C \) \textit{albicans} + \( C \) \textit{guilliermondii} and \( C \) \textit{albicans} + \( C \) \textit{krusei}.

\(^{b}\)Not otherwise specified.
### Table 3: Baseline characteristics of candidemia patients stratified by the underlying species

|                      | Candida albicans | Candida glabrata | Candida tropicalis | Candida guilliermondii | Candida krusei | Candida lusitaniae | Candida parapsilosis | Candida pseudotropicalis | Candida spp. |
|----------------------|------------------|------------------|-------------------|-----------------------|----------------|-------------------|-----------------------|--------------------------|--------------|
| **Sex**              |                  |                  |                   |                       |                |                   |                       |                          |              |
| Female               | 18               | 1                | 2                 | 1                     | 1              | 0                 | 0                     | 0                        | 3            |
| Male                 | 19               | 7                | 3                 | 55                    | 55             | 48.5              | 51                    | 47                       | 62           |
| **Age**              | (37-62)          | (48.5-67)        | (40-57)           | (55-55)               | (33-64)        | (51-51)           | (47-47)               | (31-31)                  | (32.5-67)    |
| **Charlson Comorbidity Index** | 4               | 4.5              | 3                 | 3                     | 3.5            | 5                 | 0                     | 3                        | 3.5          |
| **Underlying conditions** |                |                  |                   |                       |                |                   |                       |                          |              |
| Hem/Onc. disease     | 17               | 3                | 2                 | 2                     | 2              | 2                 | 0                     | 1                        | 2            |
| HIV/AIDS             | 1                | 2                | 0                 | 0                     | 0              | 0                 | 0                     | 0                        | 0            |
| Major surgery        | 11               | 2                | 1                 | 1                     | 1              | 1                 | 0                     | 0                        | 2            |
| Alcoholism           | 2                | 1                | 0                 | 0                     | 0              | 0                 | 1                     | 0                        | 0            |
| Chr. cardiovascular disease | 12            | 4                | 2                 | 4                     | 1              | 1                 | 1                     | 1                        | 2            |
| Chr. liver disease   | 5                | 3                | 2                 | 0                     | 0              | 0                 | 0                     | 0                        | 1            |
| Chr. pulmonary disease | 1            | 2                | 1                 | 0                     | 0              | 0                 | 0                     | 0                        | 0            |
| Chr. renal disease   | 3                | 0                | 1                 | 0                     | 1              | 0                 | 0                     | 0                        | 0            |
| Diabetes mellitus    | 4                | 1                | 1                 | 0                     | 0              | 0                 | 0                     | 0                        | 0            |
| Rheumatic diseases   | 3                | 8.1              | 0                 | 0                     | 0              | 0                 | 0                     | 0                        | 0            |
| Autoimmune disorder  |                  |                  |                   |                       |                |                   |                       |                          |              |
| Obesity (BMI >30)    | 2                | 5.4              | 0                 | 0                     | 0              | 0                 | 0                     | 0                        | 0            |
| Underweight (BMI <18.5) | 4             | 1.8              | 2                 | 0                     | 0              | 0                 | 0                     | 0                        | 1            |
| CVC                  | 33               | 8.9              | 1                 | 1                     | 1              | 1                 | 1                     | 1                        | 4            |
| ICU stay             | 23               | 62.2             | 1                 | 4                     | 1              | 1                 | 1                     | 0                        | 3            |
| MV                   | 15               | 40.5             | 1                 | 3                     | 0              | 1                 | 1                     | 0                        | 0            |
| Trauma               | 2                | 5.4              | 0                 | 0                     | 0              | 0                 | 0                     | 0                        | 0            |
| IV drug abuse        | 0                | 0.0              | 1                 | 0                     | 0              | 0                 | 0                     | 0                        | 0            |
| Other risk factors*  | 4                | 10.8             | 2                 | 1                     | 0              | 0                 | 0                     | 0                        | 0            |

Note: Three patients had a mixed infection of two Candida species: Candida albicans + Candida glabrata, Candida albicans + Candida guilliermondii and Candida albicans + Candida krusei

Abbreviations: BMI, body mass index; CCI, Carlson comorbidity index; Chr, chronic; CVC, central venous catheter; Hem/Onc., haematology/oncology; HIV/AIDS, human immunodeficiency virus infection / acquired immunodeficiency syndrome; ICU, intensive care unit; iv, intravenous; MV, mechanical ventilation.

*Candida albicans*: aortic aneurysm + aortal prosthesis, Tenckhoff catheter, Ventriculo-peritoneal stunt, and vascular stent (n = 1, each). *Candida glabrata*: cardiac pacemaker and jejunal tube (n = 1, each). *Candida tropicalis*: aortic prosthesis (n = 1).
were treated for 14 days after first negative follow-up blood culture whereas only 13.6% of non-survivors were treated in the same manner ($P = .003$). CVCs were removed in 72.4% of survivors and 64.7% of non-survivors ($P = n.s.$), and follow-up blood cultures were performed in 82.8% and 63.6% of surviving and non-surviving patients ($P = .003$; Table 5).

### 3.7 | Mortality

During our study period, we observed an in-hospital mortality of 33.3% for candidemia cases (17/51) and 11.8% for control patients (6/51). Day 30 mortality rates for cases and controls were 23.5% (12/51) and 7.8% (4/51) respectively. The attributable mortality of candidemia therefore was 21.5%. Attributable Day 30 mortality was 15.7%. In case of a fluconazole-resistant *Candida* isolate causing the bloodstream infection, the overall mortality was 27.3% (3/11). Figures 1 and 2 provide Kaplan-Meier analysis of patients and controls (Figure 1) and survival according to *Candida* species (Figure 2).

### 4 | DISCUSSION

We performed a retrospective, single-centre, matched-pair study analysing the attributable mortality in patients with nosocomial candidemia from 1997 to 2001.

Our study observed a lower attributable mortality than studies previously performed in Iowa during the same period (21.5% vs 49%) and from 1983 to 1986 (38%).2,3 Overall mortality in candidemia patients was significantly lower in our study (33% vs 61%) whereas mortality in control patients was similar (11.8% vs 12%).2

Our prior single-centre study showed higher case / control in-hospital-mortality rates in comparison with our more recent study (cases 33.3% vs 43%, controls 11.8% vs 17%; attributable mortality 21.5% vs 26%).13 Furthermore, comorbidity rates and overall candidemia incidence were lower in our study (3.5/10 000 admissions vs 6/10 000 admissions).13 Higher morbidity and mortality rates in more recent publications could be explained by the demographically changing society.1 A retrospective analysis including all episodes of candidemia from 2004 to 2015 in Belgium observed a significant increase of the incidence of candidemia over the study period.17

A Swiss study, including all national university hospitals, described an incidence of 3.6 episodes per 10 000 hospital admissions in 2000, which is in accordance with the incidence of 3.5 per 10 000 admissions observed in our study.5 Similar results have been published in French and Italian studies.18,19 A Slovenian study including all candidemia cases between 2001 and 2012 in two hospitals described an incidence of 3.2 per 10 000 admissions.20

Comorbidity rates reported by Gudlaugsson et al were higher compared to our study (CCI median for cases and controls 3.3 and 3.4 vs 3.0 and 3.0) as was the incidence of candidemia (5.2/10 000 admissions).

### 3.6 | Guideline adherence

Diagnostic procedures were provided to more survivors than to non-survivors, in particular susceptibility testing (17.1% vs 4.5%, $P = .404$) and ophthalmoscopy (28.6% vs 0%, $P = .005$). 45.7% of survivors

### TABLE 4 Antifungal therapy

| Antifungal therapy, n (%) |       |
|--------------------------|-------|
| Amphotericin B           | 13 (22.8%) |
| Amphotericin B deoxycholate | 12 (21.1%) |
| Liposomal Amphotericin B | 1 (1.8%) |
| Triazoles                | 48 (84.2%) |
| Fluconazole              | 47 (82.5%) |
| Voriconazole             | 1 (1.8%) |
| Study medication         | 1 (1.8%) |
| Study medication (MK 0991 vs placebo or liposomal Amphotericin B vs Placebo – empiric treatment) | 1 (1.8%) |

| Length of treatment in days, median (IQR) | 16 (11-29) |
| Treatment sequence, n (%) |       |
| Single monotherapy       | 41 (71.9%) |
| Single therapy sequential| 7 (12.3%)  |
| Single + combined therapy | 2 (3.5%)  |
| Combined therapy         | 1 (1.8%)  |
| No antifungal therapy     | 3 (5.3%)  |
| Unknown                   | 3 (5.3%)  |

| Treatment strategies, n (%) |       |
| Antifungal treatment        | 22 (38.6%) |
| Antifungal treatment + CVC removal | 29 (50.9%) |
| CVC removal                | 1 (1.8%)  |
| No treatment               | 2 (3.5%)  |
| Unknown                    | 3 (5.3%)  |

a Two of them died.
b Due to death.
admissions vs 3.5/10 000 admissions). This is in accordance with studies performed in Europe and the United States, which reported a higher incidence of candidemia in the United States compared to European countries. Between 2002 and 2004, the incidence of candidemia in the United States was between 4.6 and 7 per 10 000. Amphotericin B deoxycholate and fluconazole were the treatment of choice for candidemia between 1997 and 2001. Our study shows a lower share of amphotericin B treatment with a rate of 22% vs 65% for amphotericin B monotherapy and 28% vs 40% for amphotericin B plus fluconazole compared to the studies performed by Gudlaugsson et al. Mortality rates observed in our study are similar to a multicentre, prospective, observational study of 427 consecutive patients with candidemia, performed in 1995 in the United States which observed a crude mortality of 34%. A large study analysing patients with nosocomial BSI between 1995 and 2002 in the United States reported a crude mortality rate of candidemia of 39.2%. A study analysing candidemia in five centres in Scotland and Wales in 2008 described an overall mortality of 40.4%. Median age at the onset of candidemia was 55 years in our analysis. Case patients hospitalised in Iowa, US, during the same time period were in average 9 years younger with a median of 45.8 years. Median age of candidemia patients in our more recent study was 62 years. We observed a similar species distribution as previously published by Gudlaugsson et al and Cornely et al (C albicans 65% vs 63% vs 57%, C glabrata 12% vs 17% vs 17%, C tropicalis 9% vs 9% vs 9%, C parapsilosis 2% vs 12% vs 9%).

CVCs at least two days before Day 0 were present in 80% of cases (41/51) and only 33% of controls (17/51), illustrating the high impact of the presence of CVC on development and outcome of candidemia. A prospective multicentre case-control study including 118 cases and 236 controls pointed out that CVCs are one of the major risk factors for development of candidemia. A study performed in 1995 in Texas, US, including 206 patients with candidemia, showed that removal of all intravascular lines was associated with a reduction in the subsequent mean duration of candidemia from 5.6 ± 0.8 to 2.6 ± 0.5 days (P < .001). In our study, mortality rates of the patients with CVC removal within 72h vs >72h were 34% (11/32) vs 30% (3/10) respectively. CVCs were removed in 72% of survivors and 65% of non-survivors within 72h. Need of intensive care medicine is one of the major risk factors for the development of candidemia. A retrospective study collecting data from 1256 ICUs in 76 countries in 2011 reported a candidemia incidence of 69/10 000 ICU patients. A Belgian study observed a 10-fold higher incidence of candidemia in ICUs.

### Table 5: Guideline adherence in surviving and non-surviving candidemia patients

| Procedure                                      | Survivors (n = 35) | Non-Survivors (n = 22) | P-value |
|------------------------------------------------|--------------------|------------------------|---------|
| **Diagnostic**                                 |                    |                        |         |
| Initial blood culture                          | 100%               | 100%                   | 1.000\(^a\) |
| Species identification                         | 100%               | 100%                   | 1.000\(^a\) |
| Susceptibility testing                         | 17.1% (6/35)       | 4.5% (1/22)            | .404\(^b\) |
| Echocardiography                               | 31.4% (11/35)      | 27.3% (6/22)           | .738\(^a\) |
| Ophthalmoscopy                                 | 28.6% (10/35)      | 0% (0/22)              | .005\(^b\) |
| **Treatment**                                  |                    |                        |         |
| Treatment for 14 days after first negative follow-up | 45.7% (16/35)      | 13.6% (3/22)           | .020\(^b\) |
| **CVC removal**                                |                    |                        |         |
| All                                            | 96.6% (28/29)      | 82.4% (14/17)          | .825\(^b\) |
| <24 h from diagnosis                           | 55.2% (16/29)      | 41.2% (7/17)           |         |
| >24 h and <72 h from diagnosis                 | 17.2% (5/29)       | 23.5% (4/17)           |         |
| >72 h from diagnosis                           | 24.1% (7/29)       | 17.6% (3/17)           |         |
| Patient died or unknown                        | 3.4% (1/29)        | 17.6% (3/17)           |         |
| **Follow-up blood culture**                    |                    |                        |         |
| On at least one different day                  | 11.4% (4/35)       | 13.6% (3/22)           | .207\(^b\) |
| Until proven negative                          | 71.4% (25/35)      | 50% (11/22)            |         |
| No follow-up blood culture or unknown          | 17.1% (6/35)       | 36.4% (8/22)           |         |

Abbreviation: CVC, Central venous catheter.

\(^a\)Chi-square test was performed.

\(^b\)Fisher’s exact test was performed.

\(^c\)One of them died.

\(^d\)Five of them died.
FIGURE 1  Survival of patients with and without candidemia (Kaplan-Meier analysis for 365 days)

| Candida Species          | Number of patients at risk | Observation time (days) |
|--------------------------|---------------------------|-------------------------|
| Candida albicans         | 36 17 12 12 12 12 12 12 12 10 | 0 40 80 120 160 200 240 280 320 360 |
| Candida glabrata         | 6 4 4 3 3 3 3 3 3 3 | |
| Candida tropicalis       | 4 2 2 1 1 0 0 0 0 0 | |
| Candida otherwise specified | 7 7 6 4 4 3 2 2 2 2 | |

a Not otherwise specified

FIGURE 2  Survival of patients by Candida species (Kaplan-Meier analysis for 365 days)

| Candida Species          | Number of patients at risk | Observation time (days) |
|--------------------------|---------------------------|-------------------------|
| Candida albicans         | 36 17 12 12 12 12 12 12 12 10 | 0 40 80 120 160 200 240 280 320 360 |
| Candida glabrata         | 6 4 4 3 3 3 3 3 3 3 | |
| Candida tropicalis       | 4 2 2 1 1 0 0 0 0 0 | |
| Candida otherwise specified | 7 7 6 4 4 3 2 2 2 2 | |

a Not otherwise specified
compared to normal wards (7.22 vs 0.69 episodes per 10 000 patient days respectively) between 2004 and 2015.11 In our study, more case than control patients were hospitalised on ICU at least two days before d0 (31.4% vs 13.7%) and were treated on ICU for a longer time period (median 23.5 days vs 15 days). 21.6% of cases and 11.8% of controls needed mechanical ventilation. The first clinical practice guideline was published by the IDSA in 2000, one year before the end of our observation period.11 The lacking or not yet well-established guidelines might be the reason for a less consistent treatment management in our study. During the time of our observational period, susceptibility testing at the UHC had not yet been implemented as a standard of care; therefore, only 7 of 57 isolates were tested.

Our study is limited by several factors. These include the retrospective study design, selection bias and a small study population. Due to incomplete data sets and hindered legibility of microfilmed files, relevant information was incomplete or not available in eight cases: five of them had to be excluded from our study, and in three cases, we could not retrieve any information about antifungal treatment or management of central lines. However, these three patients were not excluded from our study. We tried to eliminate confounding effects by performing a precise matching process. Due to enhanced knowledge about risk factors, matching procedure was more accurate compared to Gudlaugsson et al: treatment on ICU became one of the main selection criteria. However, out of 57 case patients, only 51 could be matched to suitable control patient. Treatment on ICU at least two days before Day 0 was a risk factor present in 29.4% of cases but only 13.7% of controls. Still, to every case patient treated on ICU on Day 0, a control patient with admission on ICU within 14 days was matched. In eight cases, patients could not be matched by length of time at risk until Day 0. In these cases, time of risk was shorter for control patients.

Our study showed that crude and attributable mortality rates of candidemia at the UHC before the introduction of echinocandins were slightly lower than after their introduction. Thus, despite a higher efficiency of available antifungals, the attributable mortality did not decrease. Due to a higher morbidity of patients in a demographically changing society, the incidence of candidemia increased over the last decade. In our study, we observed a significantly lower attributable mortality compared to the study performed in Iowa, US, in the same time period. This might be driven by a lower comorbidity rate in case patients and a lower incidence of candidemia in our study. Furthermore, the preferential usage of amphotericin B over triazoles in the study population of Gudlaugsson et al might be a contributing factor. In several studies, amphotericin B deoxycholate is shown to be as effective but more toxic than fluconazole,26–28 although these studies could not identify a difference in survival. The combination of amphotericin B with fluconazole is as effective as fluconazole alone but more toxic.29

An improved disease management, including aspects recommended by the IDSA Guideline from 2000 like follow-up blood cultures, treatment for 14 days after first negative follow-up blood culture and removal of CVCs,11 might also improve morbidity rates. Improved diagnostic and prophylactic procedures as well as a better disease management by adherence to current guidelines contribute to a better outcome of candidemia.

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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS

Yael Blankenheim: Data curation (lead); Formal analysis (lead); Investigation (lead); Writing – original draft (lead); Writing – review & editing (lead). Jon Salmant-García: Formal analysis (equal); Investigation (equal); Methodology (equal); Writing – original draft (supporting); Writing – review & editing (supporting). Harald Seifert: Investigation (supporting); Writing – original draft (supporting); Writing – review & editing (supporting). Oliver A. Cornely: Conceptualization (lead); Formal analysis (supporting); Methodology (lead); Writing – original draft (equal); Writing – review & editing (equal). Philipp Koehler: Conceptualization (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Supervision (lead); Writing – original draft (lead); Writing – review & editing (lead).

ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted in the author's guideline page, have been adhered to.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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