ORIGINAL RESEARCH

Intensive care unit-related fluconazole use in Spain and Germany: patient characteristics and outcomes of a prospective multicenter longitudinal observational study

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Background: *Candida* spp. are a frequent cause of nosocomial bloodstream infections worldwide.

Objective: To evaluate the use patterns and outcomes associated with intravenous (IV) fluconazole therapy in intensive care units in Spain and Germany.

Patients and methods: The research reported here was a prospective multicenter longitudinal observational study in adult intensive care unit patients receiving IV fluconazole. Demographic, microbiologic, therapy success, length of hospital stay, adverse event, and all-cause mortality data were collected at 14 sites in Spain and five in Germany, from February 2004 to November 2005.

Results: Patients (n = 303) received prophylaxis (n = 29), empiric therapy (n = 140), preemptive therapy (n = 85), or definitive therapy (n = 49). A total of 298 patients (98.4%) were treated with IV fluconazole as first-line therapy. The treating physicians judged therapy successful in 66% of prophylactic, 55% of empiric, 45% of preemptive, and 43% of definitive group patients. In the subgroup of 152 patients with proven and specified *Candida* infection only, 32% suffered from *Candida* specified as potentially resistant to IV fluconazole. The overall mortality rate was 42%.

Conclusion: Our study informs treatment decision makers that approximately 32% of the patients with microbiological results available suffered from *Candida* specified as potentially resistant to IV fluconazole, highlighting the importance of appropriate therapy.

Keywords: antifungal agents, *Candida*, fungal infection, therapy

Introduction

Candida spp. are a frequent cause of nosocomial bloodstream infections worldwide.[1–7] *Candida albicans* is the most prevalent species found in blood cultures, although an increasing proportion of *Candida* bloodstream isolates due to non-*albicans Candida* have also been reported in many countries.[8,9] The most frequent non-*albicans Candida* spp. reported in Spain and Germany have been found to be *C. parapsilosis* and *C. glabrata*, respectively.[6,10]

Despite the frequency of occurrence of invasive candidiasis and the high associated mortality rates, this condition remains difficult to diagnose because of the prevalence of colonization without accompanying infection, nonspecific symptoms, and variable presentation. Diagnosis is therefore increasingly based on surrogate markers such as persistent pyrexia despite broad-spectrum antibiotic use, raised serum C-reactive protein, and the presence of other individual risk factors.[1,4,11]

Once a diagnosis is made, azoles, polyenes, or echinocandins are typically selected for treatment. Many agents have efficacy- or safety-related limitations. Drug resistance and lack of coverage of non-*albicans Candida* is an issue with fluconazole.[8,12,13] Amphotericin B products are associated with renal and other toxicities,[14,15] while drug interactions are common with itraconazole and voriconazole.[3,16] Once an agent is selected, it is necessary to determine whether the patient requires antifungal prophylaxis, empiric therapy, preemptive therapy, or definitive (sometimes referred to as "targeted") antifungal therapy.[4]

Definitive evidence supporting the use of these strategies in the intensive care unit (ICU) is lacking. While a few studies have shown that fluconazole therapy may be beneficial when used in certain critically ill surgical ICU patients,[1,17–19] treatment failure was observed more often in studies that also included *C. krusei* infections.[20,21] Moreover, some studies indicate that prophylactic and empiric use of fluconazole may shift the flora towards non-*C. albicans* with decreased susceptibility to fluconazole.[22] In a recently published French study, in vitro susceptibility to fluconazole was higher in patients naive to azole agents (84%) than in patients previously exposed to azole agents (70%).[9]

The morbidity, mortality, and health care costs associated with invasive fungal infections warrant further exploration in the ICU patient population to determine the effectiveness of prophylaxis as well as empiric, preemptive, and definitive therapies. To begin addressing these issues, we conducted a prospective study to evaluate the utilization patterns and outcomes associated with intravenous (IV) fluconazole therapy within hospital ICUs in Spain and Germany. The epidemiological results as well as clinical and therapeutic aspects of the study are presented in this paper.

Patients and methods
Study design and patient population

This prospective multicenter longitudinal real-world observational study was designed to collect demographic, all-cause mortality, therapy response, and length of hospital stay data on adult ICU patients receiving IV azole therapy for the treatment of fungal infections. The study was conducted at 19 sites, 14 in Spain and five in Germany, from February 2004 to November 2005. Study patients were observed until discharge from the hospital or death, so that the data collection period was dependent on the length of hospital stay. The study was submitted to the responsible ethics committees in accordance with local regulations, and a positive decision (approval) was made: in Germany, by the Ethical Review Board of the Bavarian State Chamber of Physicians, Munich, Germany (Bayerische Landesärztekammer Ethik Kommission Nummer 03099) and, in Spain, by the Ethical Review Board of the of the Bellvitge Hospital, Barcelona, Spain (Comité Ético De Investigación Clínico ref 225/03). Data collection was conducted in accordance with the ethical standards outlined in the *Declaration of Helsinki*[23] and *Guideline for Good Clinical Practice*.[24]

Eligible patients were those who were admitted to the ICU or surgical ICU during the study period, initiated an azole intravenously during ICU/surgical ICU admission, were between 18 and 100 years old, had signed informed consent, and were not on an investigational azole. Attending physicians were responsible for selecting the antifungal therapy.

Study procedures
Efficacy and safety assessments

Internet-based electronic case report forms were used to collect patient data. Demographic characteristics included age, weight, sex, race, and medical history. Antifungal treatment characteristics (prophylaxis; empiric, preemptive, and/or definitive therapy),[4] drugs received, and duration of therapy were recorded. Information on comorbidities and predisposing risk factors was collected. Severity of illness measures, including Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and Sequential Organ Failure Assessment (SOFA) scores, were calculated for all patients at the start of IV fluconazole therapy. Microbiological information included dates, type, site of cultures (primarily sterile or primarily non-sterile), and identification of isolates. Location and duration of hospital stay from initiation of IV fluconazole treatment to hospital discharge, hospital discharge diagnosis, and clinical outcomes and mortality were also recorded. Drug interactions and adverse events were recorded for all concomitant medications administered during the ICU stay while the patient was receiving IV fluconazole.

During a hospital stay, antifungal therapy may often change for a patient. Therefore, the number of treatment cycles within a hospital stay with fluconazole and non-fluconazole was determined. A "treatment cycle" was defined as a period of consecutive use of a particular antifungal drug, with no further specification regarding duration or dose, since this was an observational study.

During the course of treatment, cultures from primarily sterile and primarily non-sterile sites were collected for isolate identification from each patient at the time the treating physician decided to perform microbiological testing as

part of routine practice. Fungal cultures were incubated and isolates identified according to standardized procedures at the individual site.

Definitions of therapeutic response

All prophylaxis and therapy definitions were made prospectively during the initial study design according to the Revised 1994 British Society for Antimicrobial Chemotherapy Working Party definitions, as described by Flanagan and Barnes.[4] The treating physician was responsible for assigning individuals to one of these categories based on clinical and microbiological information. Predefined criteria for successful therapy according to treatment arm are depicted in Figure 1. Prophylaxis, preemptive, and empiric therapy

were considered unsuccessful if one or more of the criteria of successful treatment were not met. Definitive therapy was considered unsuccessful if there was no improvement in attributable symptoms and signs, and no improvement in attributable abnormalities detected by radiography, bronchoscopy, endoscopy, or other procedures. Successful empiric therapy also required absence of breakthrough fungal infections during the observation period – that is, the time of hospitalization. "Breakthrough infection" was defined as any identification of an isolate at least 5 days after initialization of IV fluconazole treatment in the prophylaxis and empiric therapy groups.

Finally, an assessment was made for patients with mycology results available. Based on recent literature,[9,12,13]

"Successful" therapy was defined by type of therapy.

Prophylaxis therapy was considered successful if: patients survived for 7 days after completion of IV azole therapy; there was an absence of breakthrough fungal infections during the administration of IV azole therapy or within 7 days after completion of treatment; there was an absence of premature discontinuation of the study drug because of drug-related toxicity or lack of efficacy; in case of subsequently confirmed baseline fungal infection (culture from sterile site pre-initiation of IV azole), there was resolution of all attributable symptoms and signs and in all attributable abnormalities detected by radiography, bronchoscopy, endoscopy, or other procedures; there was a negative culture for fungal pathogens that did not need to be repeated to confirm.

Successful *empiric therapy* was defined as: survival for 7 days after completion of IV azole therapy, resolution of all symptoms and signs (such as fever); absence of breakthrough fungal infections during administration of IV azole therapy or within 7 days after completion of therapy; absence of premature discontinuation of the study drug because of drug-related toxicity or lack of efficacy or drug–drug interaction; in case of subsequently confirmed baseline fungal infection (culture from sterile site pre-initiation of IV azole), resolution in all attributable symptoms and signs and in all attributable abnormalities detected by radiography, bronchoscopy, endoscopy, or other procedures; negative culture for fungal pathogens that did not need to be repeated to confirm.

Successful *preemptive therapy* (complete response) was defined as: survival for 7 days after completion of IV azole therapy; resolution of all symptoms and signs (such as fever) and resolution of radiographic, endoscopic abnormalities; microbiologic eradication of colonized sites during administration of IV azole therapy or within 7 days after completion of therapy; absence of premature discontinuation of the study drug because of drug-related toxicity or lack of efficacy or drug–drug interaction; in case of subsequently confirmed baseline fungal infection (culture from sterile site pre-initiation of IV azole), there was resolution in all attributable symptoms and signs and in all attributable abnormalities detected by radiography, bronchoscopy, endoscopy, or other procedures; negative cultures for fungal pathogens which did not require repetition for confirmation.

Definitive therapy was considered successful (complete response) if: patients survived for 7 days after completion of IV azole therapy; resolution occurred in all attributable symptoms and signs and in all attributable abnormalities detected by radiography, bronchoscopy, endoscopy, or other procedures; there was absence of breakthrough fungal infections during administration of IV azole therapy or within 7 days after completion of therapy; there was absence of premature discontinuation of the study drug because of drug-related toxicity or lack of efficacy or drug–drug interaction; cultures were negative for fungal pathogens and did not need to be repeated to confirm.

Figure 1 Predefined definitions of successful therapy according to individual treatment arm.
Abbreviation: IV, intravenous.

patients with *Candida* infection only were classified as potentially sensitive versus potentially resistant to IV fluconazole treatment by a panel of physicians and microbiologists in case mycology results had been obtained at the individual sites. *Candida* spp. were classified as potentially sensitive to fluconazole treatment (*C. albicans*, *C. parapsilosis*, and *C. guillermondii*) or potentially resistant to fluconazole treatment (*C. glabrata*, *C. krusei*, and *C. tropicalis*). Patients suffering from both species potentially sensitive and potentially resistant to fluconazole treatment were counted in the latter group. Patients having only nonspecified *Candida* spp. or non-Candida coinfection were excluded from these analyses.

Statistical analysis

An exploratory data analysis was conducted to identify predictors of successful fluconazole therapy by using a significance level of 5%. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated for the association of the individual factor with successful therapy. The following characteristics were assessed based on the judgment of the treating physician: patient age > 64 years, female sex, patient weight ≥ 70 kg, APACHE II score, neutropenic status on admission to ICU, mechanical ventilation at initiation of prophylaxis/therapy, reason for fluconazole therapy, number of IV fluconazole treatment cycles, number of non-fluconazole treatment cycles, number of cultures from primarily sterile sites, number of cultures from primarily non-sterile sites, *C. albicans* isolate, non-*albicans Candida* isolate, medical conditions (congenital disease, diabetes mellitus, endocrine disorders, ear nose throat disease and dental disease, eye problems and cataracts, gastrointestinal tract disease, genitourinary disease, heart disease, hematological disease, hypertension, liver disease, lung disease, neoplastic disease, neurologic and psychiatric disease, rheumatologic/skeletal disease, skin disease, vascular disease), length of hospital stay, drug–drug interactions and adverse events related to fluconazole therapy, risk factors (active malignancy, acute renal failure, human immunodeficiency virus, recent broad-spectrum antibiotic use, recent use of central venous catheter, diabetes mellitus, (continuous) renal replacement therapy including hemodialysis, immunosuppressive medication, neutropenia (absolute neutrophil count < 500 cells/μL), recent parenteral nutrition (hyperalimentation), prior fungal colonization, major surgery (within 30 days), trauma, solid organ transplantation, and overall number of risk factors. Model predictors were determined based on literature review and expert clinical opinion. A panel of physicians,

pharmacists, and statisticians prioritized possible predictors of successful therapy based on relevant literature.

Risk factors were preselected for the next analysis step. Variables included in the model were significant at $P \leq 0.20$ in univariate models. A backward variable selection method, with a selection level of 5%, was used to identify the list of predictors for successful therapy. ORs with 95% CIs were calculated.

Results
Patient accounting and demographics

Patients (n = 325) were enrolled in one of four treatment arms at the discretion of the individual treating physician: prophylaxis (n = 29; 10%), empiric therapy (n = 140; 46%), pre-emptive therapy (n = 85; 28%), or definitive therapy (n = 49; 16%). Three patients were excluded due to lack of treatment information. Subsequent analyses focused only on patients who received IV fluconazole during their hospitalization. This resulted in the elimination of 19 additional patients (seven from Germany and twelve from Spain) who received other azoles. Thus, data for 303 patients (112 from Germany and 191 from Spain) were analyzed.

The final cohort of 303 patients on IV fluconazole therapy had a mean age of 60 ± 16 years. The mean APACHE II score was 19 ± 10, with the widest range of scores observed in patients in the definitive therapy group (21 ± 15; Table 1). SOFA scores ranged from four to 14, with a mean of nine. Seven percent of patients had neutropenic status at ICU admission (<500 cells/μL) and 82% were on mechanical ventilation when they entered the study. Major risk factors for developing fungal infections included recent use of broad-spectrum antibiotics (95%), recent use of a central venous catheter (97%), the status of the patient's recent parenteral nutrition (67%), major surgery within 30 days (69%), and acute renal failure (47%).

Mycology

Pathogens at treatment initiation of IV fluconazole therapy or under treatment with IV fluconazole were available from 251 patients. In 131 of these 251 patients, only one species could be identified. Colonization with two species was present in 90 patients, with three species in 24 patients, and with four species in six patients. The number of patients suffering from *C. albicans*-only infection was 87 patients (35%), whereas 63 patients (25%) did not suffer from *C. albicans* at all. Thirteen patients (5%) were infected with a combination of *Candida* with non-*Candida* spp., which were mainly *Aspergillus* (nine patients, 4%).

Table 1 General patient characteristics

Parameter	All	Prophylaxis	Empiric therapy	Preemptive therapy	Definitive therapy
Total number of patients	303	29	140	85	49
Characteristic	n (%)	n (%)	n (%)	n (%)	n (%)
Age					
<65 years	162 (54%)	21 (72%)	84 (60%)	34 (40%)	23 (47%)
≥65 years	303 (47%)	8 (28%)	56 (40%)	51 (60%)	26 (53%)
Gender					
Male	209 (69%)	22 (76%)	102 (73%)	52 (61%)	33 (67%)
Female	94 (31%)	7 (24%)	38 (27%)	33 (39%)	16 (33%)
Weight					
<70 kg	79 (26%)	11 (38%)	29 (21%)	20 (24%)	19 (39%)
≥70 kg	224 (74%)	18 (62%)	111 (79%)	65 (76%)	30 (61%)
APACHE II score at start of antifungal treatment (mean ± SD)	19 ± 10	16 ± 7	19 ± 7	19 ± 8	21 ± 15
SOFA score at start of antifungal treatment (mean ± SD)	9 ± 5[a]	10 ± 5	8 ± 5	9 ± 4	7 ± 3
Neutropenic status at ICU admission < 500 cells/μL	20 (7%)	3 (10%)	14 (10%)	2 (2%)	1 (2%)
Mechanical ventilation at study entry	248 (82%)	22 (76%)	109 (78%)	75 (88%)	42 (86%)
Medical conditions before start of fluconazole therapy					
<3	94 (31%)	14 (48%)	50 (36%)	19 (22%)	11 (23%)
Risk factors for developing fungal infections					
<5	98 (32%)	4 (14%)	49 (35%)	28 (33%)	17 (35%)
Active malignancy	60 (20%)	11 (38%)	27 (19%)	10 (12%)	12 (25%)
Acute renal failure	141 (47%)	11 (38%)	62 (44%)	45 (53%)	23 (47%)
AIDS/HIV infection	9 (3%)	2 (7%)	5 (4%)	2 (2%)	0
Broad-spectrum antibiotic use immediately prior to IV fluconazole	287 (95%)	29 (100%)	130 (93%)	81 (95%)	47 (96%)
Recent use of central venous catheter	293 (97%)	29 (100%)	134 (96%)	81 (96%)	49 (100%)
Diabetes mellitus	92 (31%)	8 (28%)	37 (27%)	27 (32%)	20 (41%)
CRRT	96 (32%)	10 (35%)	42 (30%)	32 (38%)	12 (25%)
Immunosuppressive medication	51 (17%)	13 (45%)	25 (18%)	11 (13%)	2 (4%)
Neutropenia (ANC < 500 cells/μL)	20 (7%)	3 (10%)	14 (10%)	2 (2%)	1 (2%)
Recent parenteral nutrition	204 (67%)	21 (72%)	88 (63%)	60 (71%)	35 (71%)
Organ transplantation	26 (9%)	13 (45%)	10 (7%)	2 (2%)	1 (2%)
Prior fungal colonization	34 (11%)	1 (3%)	15 (11%)	13 (15%)	5 (10%)
Major surgery (within 30 days)	210 (69%)	25 (86%)	95 (68%)	54 (64%)	36 (74%)
Trauma	42 (14%)	4 (14%)	21 (15%)	12 (14%)	5 (10%)

Notes: Data are % of patients, unless otherwise indicated; [a]n = 148.
Abbreviations: AIDS/HIV, acquired immunodeficiency syndrome/human immunodeficiency virus; ANC, absolute neutrophil count; APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, (continuous) renal replacement therapy including hemodialysis; ICU, intensive care unit; IV, intravenous; SOFA, Sequential Organ Failure Assessment.

The microbiology results of the 407 isolates are shown in Table 2. To sum, *Candida* was the most common isolate (393/407 isolates, 96.5%), with *C. albicans* in 190 isolates (46.6%), non-*albicans Candida* in 92 isolates (22.6%), and nonspecified *Candida* in 111 isolates (27.3%). *Aspergillus* was the most prominent non-Candida isolate (n = 10; 2.5%).

Fluconazole therapy

Patients started antifungal therapy within 20.1 ± 16.8 days of being admitted to hospital and had their initial fluconazole therapy in 15.3 ± 15.1 days of being admitted to the ICU for the first time (Table 3). For 263/303 patients with at least one documented treatment dose available, the overall mean (median; minimum [min]/maximum [max]) loading dose

was 648 mg/day (400 mg; 100 mg/1200 mg), and the highest follow-up prophylaxis/treatment dose was 543 mg/day (400 mg; min 50 mg/max 1600 mg). The mean loading and follow-up dose were (n = 17/29) 600 mg (400 mg; min 200 mg/max 1200 mg) and 438 mg (400 mg; 50 mg/800 mg) for prophylaxis; for empiric therapy (n = 113/140), 650 mg (400 mg; min 100 mg/max 1200 mg) and 565 mg (400 mg; min 100 mg/max 1600 mg); for preemptive therapy (n = 84/85), 661 mg (400 mg; min 200 mg/max 1200 mg) and 537 mg (min 200 mg/max 1200 mg); and for definitive therapy (n = 49/49), 637 mg (400 mg; min 200 mg/max 1200 mg) and 539 mg (400 mg; min 200 mg/max 800 mg). A total of 298 patients (98%) initiated IV fluconazole as first-line therapy; 111 (99%) were from Germany and 187 (98%) were from Spain.

Table 2 Pathogens (n = 407) isolated at initiation or on intravenous fluconazole treatment in 251 patients with mycology results available

Pathogen	Number of isolates	%	% of all specified Candida[a]
Candida	393	96.5	
C. albicans	190	46.6	67.4
C. glabrata	38	9.3	13.5
C. krusei	9	2.2	3.2
C. tropicalis	25	6.1	8.9
C. parapsilosis	19	4.7	6.7
C. guillermondii	1	0.3	0.3
C. not specified	111	27.3	
Aspergillus	10	2.5	
Other fungi[b]	4	1.0	
Total	407	100.0	

Notes: [a]Includes *C. albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, *C. guillermondii* (n = 282); [b]includes *Mucor*, *Scedosporium*, *Trichosporon*.

The remaining five patients who received fluconazole as second-line therapy had received oral fluconazole (n = 2), amphotericin B (n = 1), liposomal amphotericin B (n = 1), and caspofungin (n = 1) as first-line therapy. All patients in the prophylaxis and empiric therapy groups had IV fluconazole as first-line therapy, while 99% of patients in the preemptive therapy group and 92% of patients in the definitive therapy group had IV fluconazole as first-line therapy.

The mean length of hospital stay for patients from initiation of IV fluconazole therapy to ICU and hospital discharge was 12.7 ± SD 16.1 days and 37.9 ± SD 46.9 days, respectively.

There were 124 adverse events related to fluconazole therapy in 31 of 303 patients (10.2%; of these, 22 were clinical [18%] and 102 were laboratory [82%]). In 17 patients, fluconazole interacted with concomitant medications.

The overall mortality rate for this study was 42% (n = 127).

Outcomes of fluconazole therapy by type of therapy

Based on the judgment of the individual physician, prophylaxis was successful in 19 of 29 patients (66%, 95% CI 45%–82%) and empiric therapy was successful in 77 of 140 (55%, 95% CI 46%–63%) patients. In the preemptive therapy group, complete response was present in 38 of 85 patients (45%, 95% CI 33%–59%). Complete response to definitive therapy was evident in 21 of 49 patients (43%, 95% CI 42%–58%; Figure 2). Overall, the success rate was 51% (78/152, 95% CI 43%–60%; Table 4).

In the prophylaxis and empiric therapy groups, 14/29 and 101/140 patients, respectively, had at least one mycology result available. Breakthrough infections, clinically and/or microbiologically identified after at least 5 days of IV fluconazole therapy were present in ten patients (71% of the 14 patients with mycology results available and 34% of all 29 patients) in the prophylaxis group and in 38 patients (60% of the 63 patients with mycology results available and 27% of all 140 patients) in the empiric therapy group. In patients with proven *Candida* infection, the proportion of patients suffering from an infection of *C. glabrata*, *C. krusei* and/or *C. tropicalis* – species regarded as potentially resistant to IV fluconazole – was 32% (49/152). Overall, the success rate by sensitivity of *Candida* spp. to fluconazole was 58/103 for potentially sensitive *Candida* spp. (*C. albicans*, *C. tropicalis*, and *C. guillermondii*; 56%) and 20/49 for potentially resistant *Candida* spp. (*C. glabrata*, *C. krusei*, and *C. tropicalis*; 41%; Table 4).

Univariate analysis of association of successful therapy

An explorative data analysis was conducted. Crude ORs with corresponding 95% CIs were calculated. Statistically significant associations (ORs, with 95% CIs not including 1.0) for the entire cohort were found for 11/48 characteristics examined. Factors associated with no treatment response, or indicating that treatment response was less likely, were found for: patient age ≥ 65 years (OR 0.46), number of non-IV fluconazole treatment cycles (OR 0.42), colonization with *Candida* not specified as *C. albicans* (OR 0.40), CRRT (OR 0.36), potential drug–drug interactions (OR 0.55), and heart

Table 3 Antifungal therapy characteristics by treatment group

Characteristic	All	Prophylaxis	Empiric therapy	Preemptive therapy	Definitive therapy
Time from hospital admission to antifungal therapy (days)	20.1 ± 16.8	12.3 ± 13.2	22.4 ± 20.1	19.3 ± 13.1	19.2 ± 12.4
Time from first ICU admission to initial IV fluconazole therapy (days)	15.3 ± 15.1	7.9 ± 10.3	16.3 ± 17.4	16.2 ± 13.4	15.6 ± 11.8
Initiation of IV fluconazole therapy					
First-line	298 (100%)	29 (100%)	140 (100%)	84 (99%)	45 (92%)
Number of IV fluconazole treatment cycles	1.1 ± 0.3	1.0 ± 0.2	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3

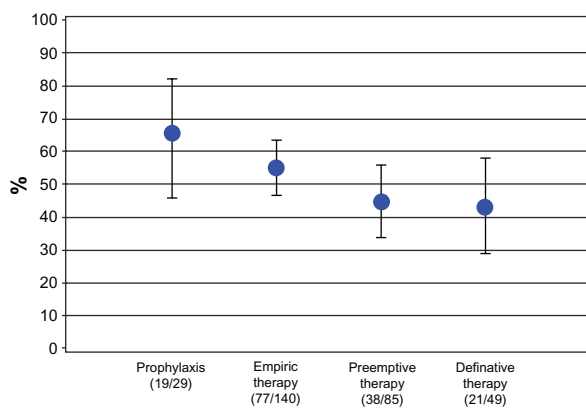**Abbreviations:** ICU, intensive care unit; IV, intravenous.

Figure 2 Complete response rates by treatment arm.

disease (OR 0.57). A high OR, indicating that treatment success is more likely, was found for recent use of central venous catheter (OR 8.60).

Multivariate analysis

Risk factors were preselected for the next analysis. Only the empiric therapy model is presented here because only this arm recruited a sufficient number of patients for multivariate analyses (Table 5). The other treatment strategies

Table 4 Treatment response by sensitivity to fluconazole treatment in 152 patients with proven *Candida* infection only

Treatment response to IV fluconazole	Potentially sensitive	Potentially resistant	Total	P*
Prophylaxis				
Failure	3	1	4	0.32
Success	6	2	8	0.16
Total	9	3	12	
Empiric therapy				
Failure	18	12	30	0.27
Success	25	9	34	0.01
Total	43	21	64	
Preemptive therapy				
Failure	12	8	20	0.37
Success	17	5	22	0.01
Total	29	13	42	
Definitive therapy				
Failure	12	8	20	0.37
Success	10	4	14	0.11
Total	22	12	34	
Total				
Failure	45	29	74	0.06
Success	58	20	78	<0.01
Total	103	49	152	

Notes: *H0:proportion = 0.5. Potentially sensitive to fluconazole treatment: *C. albicans*, *C. parapsilosis*, and *C. guillermondii*. Potentially resistant to fluconazole treatment: *C. glabrata*, *C. krusei*, and *C. tropicalis*. Patients suffering from both species potentially sensitive and potentially resistant to fluconazole treatment were counted in the latter group.
Abbreviation: IV, intravenous.

Table 5 Multivariate logistic regression for predictors of successful empiric therapy

Predictor	Point estimate (OR)	95% confidence limits
Female gender	1.54	0.55; 4.34
Colonization with *Candida* not specified as *C. albicans*	0.21	0.08; 0.54
Antibiotic use	3.93	0.43; 35.54
Major surgery within 30 days	1.70	0.60; 4.80
Immunosuppressive medication	0.37	0.10; 1.47
Recent parenteral nutrition	0.87	0.33; 2.34
CRRT	0.24	0.08; 0.70
Prior fungal colonization	9.36	1.50; 58.19
Recent use of central venous catheter	1.03	0.06; 16.59
Age ≥ 65 years	0.59	0.23; 1.52
APACHE II score	0.95	0.89; 1.01
Organ transplantation	1.26	0.13; 12.40
Diabetes mellitus	3.08	0.98; 9.70
Mechanical ventilation	0.54	0.17; 1.70
Number of fluconazole treatment cycles	5.60	0.77; 40.67
Neutropenia ANC < 500 cells/mL	4.87	0.57; 41.73

Note: Model predictors were determined based on literature review and expert clinical opinion.
Abbreviations: ANC, absolute neutrophil count; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, (continuous) renal replacement therapy including hemodialysis; OR, odds ratio.

(prophylaxis, preemptive, and definitive therapies) had sample sizes that were too small to afford multivariate analyses. A multivariate logistic regression model was created to test for the significant predictors of empiric therapy success. In the multivariate logistic model for successful treatment with empiric therapy, the significant predictors were colonization with *Candida* not specified as *C. albicans* (OR 0.21, 95% CI 0.08–0.54) and CRRT (OR 0.24, 95% CI 0.08–0.70), which were inversely associated with successful empiric therapy, and prior fungal colonization (OR 9.36, 95% CI 1.50–58.19), which was positively associated with successful empiric therapy.

Discussion

This is the largest prospective study to evaluate the real-world treatment patterns related to invasive fungal infection in the ICU setting in Spain and Germany. Many previous studies identifying potential risk factors for developing candidemia have been limited by population, which frequently involved either patients with hematologic or solid organ malignancies, and by data obtained from a single institution or over a long period of time to ensure an adequate number of cases.[25–27] Moreover, few studies were prospective in design and few focused on ICU populations.[9]

Fluconazole prophylaxis can reduce the incidence of *Candida* infection and colonization in selected critically ill patients, in both the medical and the surgical ICU settings.[2,7,17,28,29] The present study observed a complete response to IV fluconazole prophylaxis in 66% of patients. Studies have reported that early treatment with fluconazole has a favorable effect on the clinical course of high-risk patients and late antifungal treatment is associated with a poor prognosis.[11,27,30,31] Complete response rate for fluconazole in our study was comparable to studies that included all *Candida* spp.[20] but lower compared with those in which, for example, *C. krusei* was excluded.[21] However, we also observed that therapeutic success was strongly associated with type of fluconazole therapy, with empiric, preemptive, and definitive therapies being less successful and associated with higher mortality rates. It should be mentioned that the number of prophylaxis patients in our study was lower than in the treatment groups but patients were younger and differed with regard to the risk factors of acquired immunodeficiency syndrome/human immunodeficiency virus, use of immunosuppressive medications, and major surgery, which were relatively higher in number in the prophylaxis group compared with in the treatment groups. In addition, as fluconazole prophylaxis does not resolve resistant and non-*albicans Candida* infections, this may contribute to the low response rates in our cohort. At least one isolate potentially resistant to IV fluconazole was identified in 86/407 isolates (21%). In patients with at least one isolate identified, a breakthrough infection was found in 34% of all patients receiving prophylaxis with IV fluconazole and in 27% of all patients receiving empiric therapy. Very recently, in a French group studied over similar period, non-*albicans Candida* spp. (ie, *C. glabrata*, *C. parapsilosis*, *C. krusei*, and *C. tropicalis*) comprised almost half of the *Candida* isolates and reduced susceptibility to fluconazole was observed in 17.1% of *Candida* isolates.[9]

Interestingly, in 13 of 251 patients (5%), non-*Candida* fungal infection was diagnosed at least once, mainly *Aspergillus*. This is in accordance with recently published data reporting a rate of 6.7% for *Aspergillus* in the ICU.[32] This certainly warrants further investigation.

It has been suggested that early therapy be initiated in high-risk patients due to the high mortality, prevalence of invasive candidiasis, and poor reliability of available diagnostic methods.[29,33–35] The present study shows that empiric antifungal treatment is common in the ICU setting in Spain and Germany. While an expert panel of the Infectious Disease Society of America no longer favors first-line fluconazole treatment in patients with moderately severe to severe illness or patients who have had recent azole exposure,[34] European recommendations, which were valid at study initiation, focused on the use of fluconazole.[29] The British Society for Antimicrobial Chemotherapy Working Party has recommended empiric therapy for surgical and ICU patients thought to have deep candidiasis but for whom microbiologic, histologic, or serologic confirmation cannot be obtained.[35] This is also addressed in the most recent guidelines of the European Society of Clinical Microbiology and Infectious Diseases, which in addition downgraded fluconazole recommendation in non-neutropenic patients from AI to CIII.[36] In our study, CRRT and colonization with *Candida* not specified as *C. albicans* were the only significant negative predictors of successful therapy in the multivariate empiric model, the only arm with sufficient sample size to conduct multivariate analysis. The risk factor "prior fungal colonization" was associated with successful therapy. This might be regarded as a positive bias in our study, as the treating physician had been alerted that this was a possible reason for clinical signs of unknown origin. Finally, recent use of central venous catheter could not be confirmed as a positive predictor of successful therapy outcome by multivariate analysis.

Many studies have reported a steady increase in the number and prevalence of non-*albicans Candida*, which account for 40%–60% of the species reported as causes of invasive disease.[6,10,37–39] Some of these species have reduced susceptibility or intrinsic resistance to fluconazole, and the increasing use of azoles is thought to account for these changes.[1,31] A monocentric study from Spain in 226 candidemia episodes conducted from 2004 to 2009 found that previous use of fluconazole is an independent risk factor for fluconazole-resistant candidemia.[40] In the Spanish study, predictive factors for isolation of *C. glabrata* or *C. krusei* were neutropenia, chronic renal disease, and solid organ transplantation. Interestingly, the authors found a relationship between *C. krusei* and immunocompromised patients, as well as *C. glabrata* and elderly patients with underlying medical diseases.[40] A study of the evolving trends of candidiasis in an Italian ICU from the 1980s to 2000 found that the rate of invasive *Candida* infections and colonization appeared stable, but there were an increased number of mixed colonizations (39% versus 6%), a reduction of colonization by *C. albicans* (78% versus 93%), and increased *C. glabrata* involvement (35%).[10] In the study reported here, we report mono-colonization with *C. albicans* in only 87/251 patients

(35%) with mycology results available. Prophylactic use of fluconazole can shift the flora in the ICU away from *C. albicans* toward different fungal organisms.[41] However, the use of early therapy may explain why overall candidal infection rates remained stable in both Spain and Germany.[6,10] Our data confirm the emergence of non-*albicans Candida* and moulds, pathogens potentially resistant to fluconazole, in the ICU.

Treatment failure was high in both *Candida* spp. potentially sensitive to fluconazole (44% of cases) and *Candida* spp. potentially resistant to fluconazole (59% of cases). These real-world outcomes in a heterogeneous population support findings from randomized clinical trials that also included *C. krusei* infections, reporting failure rates of 31%–64% in patients treated with fluconazole.[20,21]

Our study has several limitations, including the small sample size of most of the study arms. In addition, causality cannot be demonstrated in an observational study and the assessments were based on evaluation by the treating physician and local diagnostic and treatment standards that were not reviewed by a panel. Information regarding the rationale for the use of fluconazole is limited and there are no data on detecting fluconazole-resistant yeast. Moreover, data on the base line of invasive fungal infection and colonization of each center were not collected and thus could not be considered as predictors of successful therapy. Based on current guidelines,[34,36] some of the patients might not have been suitable for fluconazole treatment. Causes of the deaths were not recorded – although no death was considered related to fluconazole therapy – and the follow-up period after the end of fluconazole therapy was relatively short.

Conclusion

The prevalence of pathogens potentially resistant to fluconazole is evident in the intensive care setting in Germany and Spain. With empiric therapy being the most prevalent therapeutic strategy, more consideration needs to be given to selecting the appropriate agent for ICU patients. The importance of appropriate therapy is highlighted due to the fact that approximately 32% of the patients in our study with microbiological results available suffered from *Candida* specified as potentially resistant to fluconazole. Moreover, according to our data, fluconazole use for proven systemic *albicans* and non-*albicans Candida* infections was associated with treatment failure in about 50% of cases overall. Future studies may further help to elucidate whether early initiation of antifungal therapy with a broad-spectrum agent improves treatment outcomes in ICU populations.

Authors' contributions

Acknowledgments

Study group members

In addition to the authors of the present study, the following investigators in each country participated in the study.

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Disclosure

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