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Use of isavuconazole in critically ill patients in intensive care units: a prospective, observational, multicentre, cohort study

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Objectives: In this multicentre, prospective study, we aimed to describe the use of isavuconazole in critically ill adult patients in ICU, in terms of patient characteristics, infection characteristics and outcomes.

Methods: Prospective, observational study of ICU patients treated with isavuconazole from January 2023 to 30 April 2025 in 17 centres (ISA-SITA study within the MULTI-SITA project).

Results: A total of 177 ICU patients treated with isavuconazole were included in the study. Most patients showed at least one European Organisation for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) or FUNgal Diseases in adult patients in Intensive Care Unit (FUNDICU) host factor (141/177, 79.7%). Overall, 82/177 patients (46.3%) had either proven or probable invasive mould disease (6 and 76, respectively, mostly invasive pulmonary aspergillosis). In patients with proven or probable disease, 30-day mortality was 44.0%, and 90-day mortality was 62.2%. In multivariable analyses, SOFA score (HR 1.14 per one point increase, 95% CI 1.03–1.26, $P=0.010$) and concomitant bacterial pneumonia (HR 2.32, 95% CI 1.17–4.59, $P=0.016$) were associated with 30-day mortality, whereas prior hospitalization (HR 2.26, 95% CI 1.19–4.27, $P=0.013$) and SOFA score (HR 1.17 per one point increase, 95% CI 1.07–1.28, $P<0.001$) were associated with 90-day mortality.

Conclusions: Diverse patterns of isavuconazole use were observed in a large cohort of critically ill adult patients, and the drug was well tolerated. Mortality was lower than many previous estimates in critically ill patients and could serve as a basis for future standardized comparisons.

Introduction

Isavuconazole is a triazole agent used for the treatment of invasive aspergillosis (IA) and of mucormycosis.[1–4] These invasive mould diseases may develop in critically ill patients admitted to ICU, both in patients with and in patients without classical host factors for invasive mould diseases.[5–11]

Current experience with the use of isavuconazole in this particular population is limited for several reasons, such as (i) the difficulty of the diagnostic process (a histologically proven diagnosis is rarely available and the diagnosis is usually based on different degrees of probability conferred by the results of radiological and mycological criteria, in addition to a coherent clinical picture, such as pulmonary disease not responsive to antibiotic therapy)[9,12,13] and (ii) the frequent presence of potential alternative diagnoses (e.g. bacterial pneumonia) that can, at least initially, explain the clinical picture and reduce awareness of the possible development of IA and mucormycosis.

In this context, large cohorts describing how isavuconazole is used in critically ill patients in ICU could not only improve the positioning of isavuconazole within our diagnostic algorithms but also help to better understand which diagnostic criteria for IA and mucormycosis are used in real-life clinical practice. In turn, this could help to identify specific targets for dedicated antifungal stewardship interventions to improve the early diagnosis and treatment of IA and mucormycosis.

In this multicentre, observational, prospective study, we aimed to describe the use of isavuconazole in critically ill patients in Italian ICUs, in terms of patient characteristics, infection characteristics and outcomes.

Materials and methods

Setting and objectives

The MULTI-SITA project is a platform developed by the Italian Society of Anti-Infective Therapy (SITA) and dedicated to the conduct of observational studies on invasive bacterial and fungal diseases. ISA-SITA was an observational, prospective, multicentre study conducted in Italian hospitals within the MULTI-SITA project, registering the use of isavuconazole in consecutive critically ill patients in ICU from 17 centres. The prospective study period was from 1 January 2023 to 30 April 2025. The inclusion criterion was receipt of at least one dose of isavuconazole during the study period. Patients under 18 years of age, patients already enrolled in the study, patients not admitted to ICU and patients enrolled in investigational studies were excluded. In line with the observational nature of the study, isavuconazole was prescribed by treating physicians according to local practice, regardless of the study protocol.

The primary objective of the ISA-SITA study was to describe the use of isavuconazole in Italian ICUs (descriptive primary endpoints: characteristics of patients, characteristics of treated infections, 30-day mortality and 90-day mortality). The secondary objective of the ISA-SITA study was to assess factors associated with mortality (endpoints: 30-day mortality and 90-day mortality) in the subgroup of critically ill patients treated with isavuconazole and belonging to the following: (i) patients with proven IA/mucormycosis according to the European Organisation for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) definitions[13]; or (ii) patients with probable invasive pulmonary aspergillosis/mucormycosis according to EORTC/MSGERC definitions[13]; or (iii) patients with probable invasive pulmonary aspergillosis according to invasive FUNgal Diseases in adult patients in Intensive Care Unit (FUNDICU) definitions among patients without EORTC/MSGERC host factors.[9]

Definitions and data collected for the study

The following demographic and clinical variables were collected at the time of isavuconazole initiation: age in years; sex; prior hospital admission (within 6 months); prior ICU admission (within 6 months); admission from a long-term care facility; diabetes mellitus; New York Heart Academy (NYHA) score; chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2); chronic intermittent haemodialysis; autoimmune disease; age-adjusted Charlson comorbidity index;[14] prior antifungal therapy (within 6 months); prior antibiotic therapy (within 6 months); prior chemotherapy (within 6 months); prior major surgery (within 3 months); presence of at least one host factor for probable invasive pulmonary mould disease according to EORTC/MSGERC definitions

(recent history of neutropenia for >10 days; haematological malignancy; prolonged use of corticosteroids at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days; treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumour necrosis factor-α blockers, lymphocyte-specific monoclonal antibodies and immunosuppressive nucleoside analogues during the past 90 days; treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors; inherited severe immunodeficiency; acute graft-versus-host disease Grade III or IV involving the gut, lungs or liver that is refractory to first-line treatment with steroids)[13]; presence of at least one host factor for probable IA according to FUNDICU definitions (influenza; coronavirus disease 2019; moderate/severe chronic obstructive pulmonary disease; de-compensated cirrhosis; uncontrolled HIV infection; solid neoplasm) in patients not fulfilling EORTC/MSGERC host criteria[9]; antifungal prophylaxis with mould-active agents; days from ICU admission to isavuconazole initiation; SOFA score[15]; presence of septic shock;[16] presence of at least Stage 1 acute kidney injury (AKI) according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria[17]; invasive mechanical ventilation; continuous renal replacement therapy (CRRT); extracorporeal membrane oxygenation (ECMO); concomitant candidaemia; concomitant bacteraemia; concomitant community-acquired bacterial pneumonia (CABP), hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP); concomitant antifungal therapy for other fungal infections; and concomitant antibiotic therapy. Histological, mycological and clinical/radiological results necessary to define proven or probable IA/mucormycosis according to EORTC/MSGERC and FUNDICU definitions were also collected.[9,13] Classification according to EORTC/MSGERC and FUNDICU definitions was done by study investigators of the coordinating centre after all data were collected and before analyses were performed. The following additional data were collected regarding isavuconazole therapy: dose administered; use of therapeutic drug monitoring (TDM); type of therapy (monotherapy versus combination); concomitant use of potentially hepatotoxic drugs; drug-related adverse events (AEs) based on local investigators' judgment, including drug-related serious AEs (SAEs), if any; and length of isavuconazole therapy.

Statistical analysis

Characteristics of patients and infections treated with isavuconazole were described through proportions (%) and medians with IQR for categorical and continuous variables, respectively. The 95% CI was calculated for both proportions and median values estimates.[18,19] Cumulative 30-day mortality and 90-day mortality in the subgroup of patients with proven and probable disease, overall and stratified (in patients with probable disease) for the presence of EORTC/MSGERC host factors versus FUNDICU host factors, were summarized graphically using the Kaplan–Meier method, with time of origin set as the day of isavuconazole initiation and right-censoring in case of loss of follow-up (e.g. discharge or transfer to another hospital). In the secondary analyses of factors associated with 30-day mortality and 90-day mortality, we first performed multiple imputation by chained equations (MICEs) according to Rubin's approach, generating 10 imputed datasets using logistic regression for categorical variables and predictive mean matching for continuous variables.[20] Then, the association of demographic and clinical variables with 30-day mortality was first assessed through univariable Cox regression models. Subsequently, all variables showing a *P* value of <0.10 in univariable comparisons were included in an initial multivariable Cox regression model and further selected for inclusion in the final multivariable Cox regression model (Model A) by means of a stepwise backward procedure. Variables included in Model A were also included in an additional multivariable Cox regression model including centre as shared frailty (Model B).[21] The same process of variable selection through univariable and multivariable Cox regression, leading to inclusion in a final multivariable model (Model C), was employed for assessing variables associated with 90-day mortality. Variables included in Model C were also included in an additional multivariable Cox regression model including centre as shared frailty (Model D).[21]

The analyses were conducted using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and R Statistical Software (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria); a *p*-value less than 0.05 was considered statistically significant.

Ethics

The MULTI-SITA project was approved by the ethics committee of the coordinating centre (Liguria Region Ethics Committee, registry number 390/2020). The amendment authorizing the conduct of the ISA-SITA study within the MULTI-SITA project was approved by the Liguria Region Ethics Committee on 30 September 2022. The other participating centres followed the local ethical committee requirements and started to enrol patients prospectively once activated. All conscious patients at the time of enrolment signed an informed consent to participate in the study. A waiver of informed consent for data collection from unconscious patients at the time of enrolment due to severe clinical conditions was obtained within the ethics committee approval, in line with the observational nature of the analyses and in order not to bias research results towards high cure rates and low mortality prejudicing scientific validity.

Results

Overall, 177 critically ill patients treated with isavuconazole were included in the study (Figure S1, available as Supplementary data at *JAC-AMR* Online). Their median age was 66 years (IQR 54–73) and 34.5% were female (61/177). As shown in Table 1, 86/177 patients (48.6%) had at least one host factor for probable invasive pulmonary mould disease according to EORTC/MSGERC definitions, while, among the remaining 91 patients, 55/91 (60.4%) had at least one host factor for probable invasive pulmonary aspergillosis according to FUNDICU definitions. Overall, as many as 141/177 patients showed at least one EORTC/MSGERC or FUNDICU host factor (79.7%).

As shown in Table 2, in patients with EORTC/MSGERC or FUNDICU host factors IA and mucormycosis could be classified as proven in 5/141 cases (3.5%) and as probable in 76/141 cases (53.9%), mostly caused by *Aspergillus* spp. whenever aetiological diagnosis was available. In the remaining 60/141 patients (42.6%) with EORTC/MSGERC or FUNDICU host factors whose disease could not be classified either as proven or probable (in the latter case due to lack of clinical and/or mycological criteria), isavuconazole was administered for the following suspected IA or mucormycosis: invasive pulmonary infection (47/60, 78.3%); invasive sinonasal infection (1/60, 1.7%); and indication not further specified (10/60, 16.7%). Two other patients (2/60, 3.3%) started isavuconazole for a suspected IA or mucormycosis (invasive wound/burn infection) and later received a proven diagnosis of invasive fusariosis (by *Fusarium solani* complex) and invasive pseudallescheriasis (by *Pseudallescheria boydii*).

In patients without EORTC/MSGERC or FUNDICU host factors, the disease could be classified as proven in 1/36 cases (2.8%), as an IA of wound/burn injury (Table 2). In the remaining 35/36 patients (97.2%) without EORTC/MSGERC or FUNDICU host factors whose disease could not be classified as proven or probable (in the latter case due to lack EORTC/MSGERC or FUNDICU host factors), isavuconazole was administered for suspected invasive pulmonary aspergillosis or mucormycosis in all cases (35/35, 100%). Potential, non-mutually exclusive risk factors (not constituting

Table 1. Demographic and clinical characteristics of critically ill adult patients treated with isavuconazole

Variables[a]	No. of patients	%	95% CI
Demographics			
Age in years, median (IQR)	66 (54–73)	—	62–67
Female sex	61/177	34.5	27.6–41.8
Comorbidities and medical history			
Prior hospitalization	86/165	52.1	44.2–59.9
Prior ICU admission	22/164	13.4	8.6–19.4
Admission from LTCF	2/172	1.2	0.2–4.1
Diabetes mellitus	34/177	19.2	13.9–25.6
NYHA score, median (IQR)	1 (1–2)	—	1–1
Chronic kidney disease	28/177	15.8	10.8–21.9
Chronic intermittent haemodialysis	10/176	5.7	2.9–10.0
Autoimmune disease	17/176	9.7	5.8–14.9
Age-adjusted Charlson comorbidity index, median (IQR)	4 (3–6)	—	3–4
Prior antifungal therapy	41/161	25.5	19.1–32.8
Prior azoles	18/161	11.2	6.9–16.9
Prior polyenes	13/161	8.1	4.4–13.2
Prior echinocandins	20/161	12.4	7.8–18.5
Prior antibiotic therapy	92/153	60.1	52.0–67.7
Prior chemotherapy	29/174	16.7	11.6–22.9
Prior major surgery	48/175	27.4	21.0–34.5
Presence of at least one host factor for probable invasive pulmonary mould disease according to EORTC/MSGERC definitions[b]	86/177	48.6	41.2–56.0
Presence of at least one host factor for probable invasive pulmonary aspergillosis according to FUNDICU definitions[c]	55/177	31.1	24.4–38.4
Antifungal prophylaxis with mould-active agents	12/174	6.9	3.8–11.6
Days from ICU admission to isavuconazole initiation, median (IQR)	7 (2–18)	—	6–9
SOFA score, median (IQR)	7 (5–10)	—	7–8
Presence of septic shock	56/177	31.6	25.0–38.9
Invasive mechanical ventilation	119/176	67.6	60.3–74.3
Presence of AKI	77/175	44.0	36.8–51.4
CRRT	37/176	21.0	15.5–27.7
ECMO	6/174	3.4	1.5–7.3
Concomitant candidaemia	15/173	8.7	5.0–13.7
Concomitant bacteraemia	57/175	32.6	25.9–39.9
Concomitant CABP, HABP or VABP	84/177	47.5	40.1–54.8
Additional antifungal therapy for fungal infections other than IA and mucormycosis[d]	24/176	13.6	9.2–19.4
Concomitant antibiotic therapy	155/177	87.6	81.8–92.0

AKI, acute kidney injury; CABP, community-acquired bacterial pneumonia; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; EORTC, European Organisation for Research and Treatment of Cancer; FUNDICU, invasive FUNgal Diseases in adult patients in Intensive Care Unit; HABP, hospital-acquired bacterial pneumonia; HSCT, haematopoietic stem cell transplantation; MSGERC, Mycoses Study Group Education and Research Consortium; NYHA, New York Heart Association; LTCF, long-term care facility; SOT, solid organ transplantation; VABP, ventilator-associated bacterial pneumonia.

[a]Results are presented as no. of patients/total of patients unless otherwise indicated. Number of missing values per variable were as follows: prior hospitalization ($n=12/177$); prior ICU admission ($n=13/177$); admission from LTCF ($n=5/177$); chronic intermittent haemodialysis ($n=1/177$); autoimmune disease ($n=1/177$); age-adjusted Charlson comorbidity index ($n=1/177$); prior antifungals ($n=16/177$); prior antibiotic therapy ($n=24/177$); prior chemotherapy ($n=3/177$); prior major surgery ($n=2/177$); antifungal prophylaxis with mould-active agents ($n=2/177$); SOFA score ($n=3/177$); invasive mechanical ventilation ($n=1/177$); presence of AKI ($n=2/177$); CRRT ($n=1/177$); ECMO ($n=3/177$); concomitant candidaemia ($n=4/177$); concomitant bacteraemia ($n=2/177$); additional antifungal therapy for fungal infections other than IA and mucormycosis ($n=1/177$). No missing values were registered for all other remaining variables.

[b]Non-mutually exclusive: recent history of neutropenia for >10 days ($n=23$); haematological malignancy ($n=51$); HSCT ($n=19$); SOT ($n=13$); prolonged use of corticosteroids at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days ($n=29$); treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumour necrosis factor-a blockers, lymphocyte-specific monoclonal antibodies and immunosuppressive nucleoside analogues during the past 90 days ($n=38$); treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors ($n=12$); inherited severe immunodeficiency ($n=4$); acute graft-versus-host disease Grade III or IV involving the gut, lungs or liver that is refractory to first-line treatment with steroids ($n=6$).

[c]Assessed in patients without EORTC host factors. Non-mutually exclusive host factors according to FUNDICU definitions in patients without EORCT/MSGERC host factors: influenza ($n=8$); COVID-19 ($n=18$); moderate/severe COPD ($n=23$); de-compensated cirrhosis ($n=2$); uncontrolled HIV infection ($n=0$); and solid neoplasm ($n=20$).

[d]Echinocandins ($n=21$); polyenes ($n=2$); and azoles ($n=1$).

host factors) for probable invasive mould disease in these patients were diabetes mellitus (6/35, 17.1%); chronic kidney disease (4/35, 11.4%); compensated liver cirrhosis (1/35, 2.9%); previous steroid use not fulfilling categorization as EORTC/MSGERC host factor in terms of dosage, timing and/or length of treatment (2/35, 5.7%); autoimmune diseases (5/35, 14.3%); and multiorgan failure (28/35, 80.0%).

Isavuconazole was initiated at the recommended dosage of 200 mg every 8 h for the first 48 h and then 200 mg every 24 h as maintenance therapy in 176/177 patients (99.4%). Only one patient with de-compensated liver cirrhosis started maintenance therapy at a reduced dosage of 100 mg every 24 h. TDM during isavuconazole therapy was reported in 49/177 patients

Table 2. Characteristics of proven and probable IA and mucormycosis treated with isavuconazole

Disease	No. of patients (%)	Causative agents/comments/isavuconazole MIC (when susceptibility test was performed)
Proven ($n=6$)		
Proven invasive pulmonary aspergillosis	4/6 (66.7%)	Species identified in 2/4 cases (50%): *Aspergillus fumigatus* plus *Aspergillus terreus* ($n=1$); *Aspergillus niger* ($n=1$). Histological diagnosis on lung biopsy specimens, aetiology confirmed by culture and/or tissue PCR
Proven wound/burn injury invasive aspergillosis[a]	1/6 (16.7%)	*A. fumigatus*. Diagnosis from culture of a soft tissue specimen obtained by sterile procedure
Proven sinonasal mucormycosis	1/6 (16.7%)	*Rhizopus stolonifer* (MIC of 1 mg/L). Histological diagnosis on sinonasal biopsy specimen, aetiology confirmed by culture
Probable ($n=76$)		
Probable invasive pulmonary aspergillosis according to EORTC/MSGERC definitions	45/76 (59.2)	Causative agents identified through BALF culture in 17/45 cases (37.8%): *A. fumigatus* ($n=6$); *Aspergillus flavus* ($n=2$); *Aspergillus calidoustus/ustus* ($n=1$); *Aspergillus lentulus* ($n=1$); *Aspergillus nidulans* ($n=1$); *A. niger* ($n=1$); *A. terreus* ($n=1$); species not reported/identified ($n=4$). Causative agents identified through BALF PCR (two duplicate positives) in 1/45 cases (2.2%): *A. terreus* ($n=1$). In 27/45 patients (60.0%) with negative BALF culture and BALF PCR (when performed), mycological criteria for probable invasive pulmonary aspergillosis were as follows: BALF galactomannan ≥ 1.0 ($n=20$); serum galactomannan > 1.0 ($n=4$); BALF galactomannan ≥ 0.8 and serum galactomannan ≥ 0.7 ($n=3$). MIC values available for 2/6 isolates of *A. fumigatus* (in both cases = 0.50 mg/L), for 1/1 isolates of *A. lentulus* (0.50 mg/L) and in 1/4 isolates with species not reported/identified (2 mg/L)
Probable invasive pulmonary aspergillosis according to FUNDICU definitions[b]	31/76 (40.8)	Causative agents identified through BALF culture in 14/31 cases (45.2%): *A. fumigatus* ($n=5$); *A. flavus* ($n=2$); *A. niger* ($n=2$); *A. nidulans* ($n=1$); species not reported/identified ($n=4$). In 17/31 patients (54.8%) with negative BALF culture, mycological criteria for probable invasive pulmonary aspergillosis were as follows: BALF galactomannan ≥ 1.0 ($n=17$); serum galactomannan > 0.5 ($n=0$); BALF galactomannan ≥ 1.0 and serum galactomannan ≥ 0.5 ($n=0$). MIC values available for 2/5 isolates of *A. fumigatus* (in both cases ≤ 0.25 mg/L).

BALF, bronchoalveolar lavage fluid; EORTC, European Organisation for Research and Treatment of Cancer; FUNDICU, invasive FUNgal Diseases in adult patients in Intensive Care Unit; MIC, minimum inhibitory concentration; MSGERC, Mycoses Study Group Education and Research Consortium; PCR, polymerase chain reaction.

[a]Diagnosed in a patient without EORTC/MSGERC or FUNDICU host factors.

[b]In patients without EORTC/MSGERC host factors.

(27.7%), with dosage reductions and increases registered with identical frequency in 2/177 (1.1%) and 2/177 patients (1.1%), respectively. Overall, 100 samples from these 49 patients were collected for TDM (median one sample per patient, IQR 1–3). Isavuconazole blood levels were at least once <2 mg/L and <1 mg/L in 44.9% (22/49) of patients and 10.2% (5/49) of patients, respectively, and at least once >5 mg/L in 22.4% (11/49) of patients. Isavuconazole therapy was started intravenously and orally in 166/177 (93.8%) and 11/177 (6.2%) patients, respectively. Subsequent step-down from intravenous to oral therapy was registered in 33/166 patients who started intravenous therapy (19.9%). Isavuconazole was administered as monotherapy in 163/177 patients (92.1%) and in combination with other antifungal agents administered for the same indication in the remaining 14/177 patients (7.9%). The most frequently employed companion agent was liposomal amphotericin B (9/14, 64.3%), followed by anidulafungin (3/14, 21.4%) and caspofungin (2/14 14.3%).

Cumulative mortality in patients with proven and probable AI/mucormycosis treated with isavuconazole, both overall and stratified according to EORCT/MSGERC versus FUNDICU definitions (for probable disease), is displayed graphically in Figure 1 (for 30-day mortality) and in Figure S2 (for 90-day mortality). Cumulative 30-day mortality was 44.0% (95% CI 32.8–54.6) overall and 45.7% (95% CI 30.3–59.8) versus 46.7% (95% CI 27.8–63.6) in patients with probable disease according to EORTC/MSGERC versus FUNDICU definitions, respectively (log-rank test, $P=0.8457$). Regarding 90-day mortality, it was 62.2% (95% CI 49.6–72.4) overall and 63.3% (95% CI 46.4–76.2) versus 66.6% (95% CI 42.1–82.6) in patients with probable disease according to EORTC/MSGERC versus FUNDICU definitions, respectively (log-rank test, $P=0.7278$).

The results of univariable and multivariable analyses of factors associated with 30-day mortality are displayed in Table 3. In the final multivariable model (Model A), SOFA score (HR 1.14 per one point increase, 95% CI 1.03–1.26, $P=0.010$) and concomitant

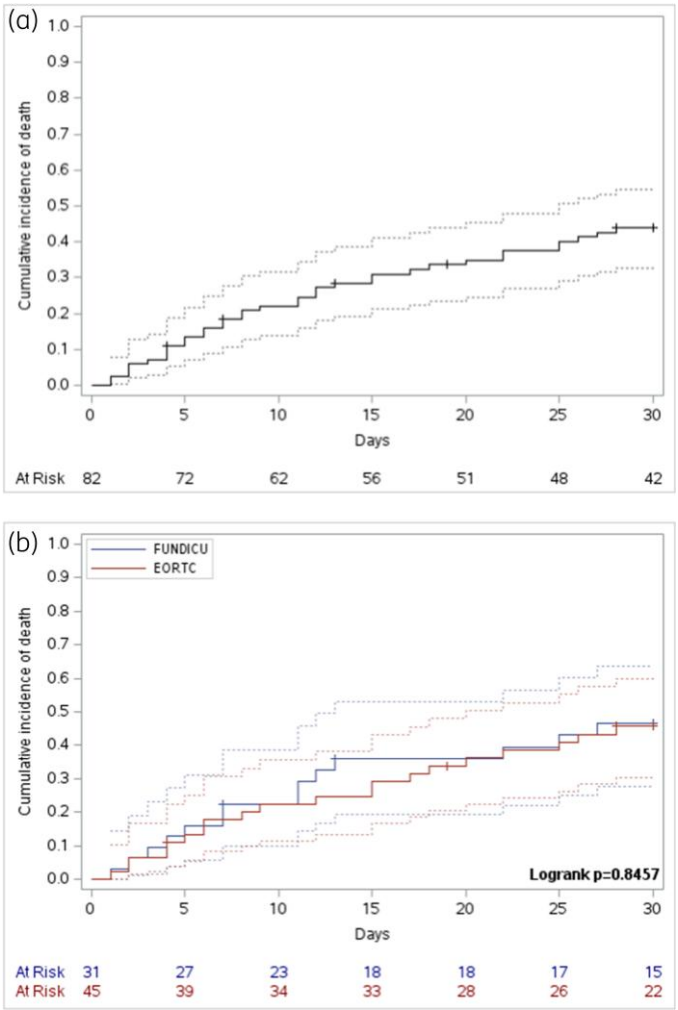

Figure 1. Cumulative mortality up to Day 30 in critically ill patients with proven and probable invasive aspergillosis/mucormycosis treated with isavuconazole. (a) Cumulative mortality up to Day 30 in ICU patients with proven or probable invasive mould disease treated with isavuconazole. (b) Cumulative mortality up to Day 30 in ICU patients with probable invasive mould disease treated with isavuconazole, stratified for classification as probable according to EORTC/MSGERC versus FUNDICU definitions. For both panels, the time of origin was set at the day of isavuconazole initiation. Death was the event of interest and right-censoring was applied at the end of follow-up (loss to follow-up before Day 30, e.g. for hospital discharge, or Day 30, whichever came first). For further details, see Materials and methods. EORTC, European Organisation for Research and Treatment of Cancer; FUNDICU, invasive FUNgal Diseases in adult patients in Intensive Care Unit; MSGERC, Mycoses Study Group Education and Research Consortium.

CABP, HABP or VABP (HR 2.32, 95% CI 1.17–4.59, $P=0.016$) retained an independent association with 30-day mortality. Results of Model B, including also centre as shared frailty, were consistent with those of Model A (Table S1). With regard to factors associated with 90-day mortality, the results of univariable and multivariable analyses are displayed in Table 4. In the final multivariable model (Model C), prior hospitalization (HR 2.26, 95% CI 1.19–4.27, $P=0.013$) and SOFA score (HR 1.17 per one point increase, 95% CI 1.07–1.28, $P<0.001$) retained and independent association with 90-day mortality. Results of Model D, including also centre as shared frailty, were consistent with those of Model C (Table S2).

Overall, drug-related AEs were reported by local investigators in 8/177 patients, all mild [diarrhoea ($n=1$), hypereosinophilia ($n=1$), hypokalaemia ($n=1$)] or moderate [hypertransaminasemia and/or hyperbilirubinemia ($n=3$), rash ($n=1$), bone marrow suppression ($n=1$)]. Of note, two out of three patients with moderate hypertransaminasemia and/or hyperbilirubinemia were receiving concomitant drugs with hepatotoxicity potential (cyclophosphamide, doxorubicin, vincristine, remdesivir and/or trimethoprim-sulfamethoxazole). No drug-related SAEs were reported. Isavuconazole was discontinued by treating physicians in 6/8 patients with mild or moderate drug-related AEs (75.0%). The median length of therapy in patients who did not discontinue isavuconazole due to drug-related AEs, who were alive at time of discontinuation and who were not lost at follow-up while still on treatment was 20 days (IQR 8–42).

Discussion

In a large, prospective, multicentre cohort of ICU patients treated with isavuconazole, most showed at least one host factor for invasive mould disease according to the EORTC/MSGERC or FUNDICU definitions. In patients with proven or probable disease, mainly IA, crude mortality (44.0% at 30 days and 62.2% at 90 days) was lower than reported in most of the current literature (often above 70%–80%),[8,11,22–26] despite the high median SOFA score and high frequency of septic shock in our cohort.

Previous studies have included critically ill ICU patients treated with isavuconazole, although most were small cohorts of less than 10 patients, or did not distinctively report the subgroup characteristics of either isavuconazole-treated or ICU patients.[27–35] Besides confirmation of the low rate of proven diagnosis of IA/mucormycosis in the ICU (only 6 among 177 treated patients), which is in line with previous literature,[36] a distinctive aspect of our study is the reporting of the fraction of patients with at least one host factor according to EORTC/MSGERC or FUNDICU definitions, which was almost 80% in our cohort. While it is somewhat striking that only less than 60% of these patients could eventually be classified as having probable disease according to EORTC/MSGERC or FUNDICU definitions, such a result was not unexpected. Indeed, both definitions, although useful for identifying patients with a high probability of true disease in clinical practice, have been primarily conceived to guarantee high specificity for inclusion in clinical trials, as a mean for increasing reliability and comparability of results across different studies.[9,13] On the other hand, the sensitivity of EORTC/MSGERC and FUNDICU definitions may remain somewhat suboptimal (i.e. some true cases of invasive mould disease may be missed), a fact that can be acceptable in research contexts for the reasons detailed above, but that also explains why some patients not fulfilling definitions are nonetheless considered for antifungal treatment in real-life clinical practice (e.g. in the absence of response to antibacterial therapy in a patient with an host factor, compatible radiological findings and a positive respiratory non-bronchoalveolar lavage fluid (BALF) galactomannan or in a patient with no host factors but less specific risk factors for IA, compatible

Table 3. Univariable and multivariable analysis of factors associated with 30-day mortality in critically ill patients with proven and probable invasive aspergillosis/mucormycosis treated with isavuconazole

	Univariable analysis		Multivariable analysis[a]	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Age in years	1.02 (0.99–1.05)	0.194		
Female sex	0.54 (0.26–1.13)	0.101		
Prior hospitalization	2.18 (1.03–4.65)	**0.043**		
Prior ICU admission	1.85 (0.81–4.21)	0.141		
Admission from LTCF[b]	—	—		
Diabetes mellitus	0.94 (0.41–2.16)	0.891		
NYHA score	1.30 (0.94–1.81)	0.114		
Chronic kidney disease	1.81 (0.82–3.98)	0.143		
Chronic intermittent haemodialysis	1.17 (0.36–3.82)	0.795		
Autoimmune disease	0.30 (0.04–2.22)	0.241		
Age-adjusted Charlson comorbidity index	1.16 (1.05–1.29)	**0.005**		
Prior antifungal therapy	1.04 (0.49–2.23)	0.914		
Prior azoles	1.70 (0.70–4.11)	0.237		
Prior polyenes	0.59 (0.15–2.39)	0.456		
Prior echinocandins	0.91 (0.35–2.36)	0.839		
Prior antibiotic therapy	0.94 (0.46–1.94)	0.871		
Prior chemotherapy	1.17 (0.51–2.68)	0.716		
Prior major surgery	1.02 (0.50–2.09)	0.952		
Probable invasive pulmonary mould disease according to EORTC/MSGERC definitions	1.09 (0.56–2.12)	0.811		
Probable invasive pulmonary aspergillosis according to FUNDICU definitions	1.18 (0.60–2.33)	0.625		
Antifungal prophylaxis with mould-active agents	0.26 (0.04–1.87)	0.178		
Days from ICU admission to isavuconazole initiation	1.00 (0.99–1.01)	0.857		
SOFA score	1.13 (1.02–1.25)	**0.016**	1.14 (1.03–1.26)	**0.010**
Presence of septic shock	2.80 (1.43–5.48)	**0.003**		
Invasive mechanical ventilation	2.25 (0.93–5.42)	0.071		
Presence of AKI	1.54 (0.79–2.99)	0.205		
CRRT	1.24 (0.56–2.73)	0.592		
ECMO	0.49 (0.07–3.55)	0.477		
Concomitant candidaemia	0.38 (0.05–2.77)	0.339		
Concomitant bacteraemia	0.74 (0.34–1.60)	0.441		
Concomitant CABP, HABP or VABP	2.17 (1.10–4.27)	**0.026**	2.32 (1.17–4.59)	**0.016**
Additional antifungal therapy for fungal infections other than IA and mucormycosis	0.98 (0.38–2.54)	0.972		
Concomitant antibiotic therapy	2.28 (0.55–9.51)	0.258		
Combination antifungal therapy	0.33 (0.08–1.39)	0.131		
Probable invasive pulmonary mould disease (versus proven IA/mucormycosis as ref.)	3.30 (0.45–21.15)	0.239		

Analyses conducted after multiple imputation (see study methods). Bold values are significant at the selected level of significance ($\alpha = 0.05$).
AKI, acute kidney injury; CABP, community-acquired bacterial pneumonia; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; EORTC, European Organisation for Research and Treatment of Cancer; FUNDICU, invasive FUNgal Diseases in adult patients in Intensive Care Unit; HABP, hospital-acquired bacterial pneumonia; NYHA, New York Heart Association; LTCF, long-term care facility; MSGERC, Mycoses Study Group Education and Research Consortium; SOT, solid organ transplantation; VABP, ventilator-associated bacterial pneumonia.
[a]Only results of the final multivariable model (Model A) after stepwise backward selection are presented. Variables included in the initial multivariable model were prior hospitalization, age-adjusted Charlson comorbidity index, SOFA score, presence of septic shock, invasive mechanical ventilation and concomitant CABP, HABP or VABP.
[b]No patients with admission from LTCF among those with proven or probable disease.

radiological findings and a positive BALF galactomannan).[37] The role of EORTC/MSGERC and FUNDICU definitions in increasing reliability and comparability of research results across different studies also explains why we reported cumulative mortality (and why we assessed risk factors for mortality) in the subgroup of patients with proven and probable disease. Indeed, outside these categories specificity would decrease, reducing the potential for generalization and comparability.

Overall, 30-day and 90-day mortality in patients with proven and probable disease in our cohort were, in most cases, lower than those previously reported in the literature for critically ill patients with IA.[8,11,22–26] This despite the large frequency of acute

Table 4. Univariable and multivariable analysis of factors associated with 90-day mortality in critically ill patients with proven and probable invasive aspergillosis/mucormycosis treated with isavuconazole

	Univariable analysis		Multivariable analysis[a]	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Age in years	1.01 (0.99–1.04)	0.313		
Female sex	0.67 (0.36–1.22)	0.186		
Prior hospitalization	1.87 (1.00–3.50)	**0.050**	2.26 (1.19–4.27)	**0.013**
Prior ICU admission	1.47 (0.69–3.14)	0.314		
Admission from LTCF[b]	—	—		
Diabetes mellitus	0.89 (0.43–1.85)	0.761		
NYHA score	1.27 (0.94–1.71)	0.121		
Chronic kidney disease	1.84 (0.91–3.72)	0.088		
Chronic intermittent haemodialysis	1.29 (0.46–3.62)	0.623		
Autoimmune disease	0.71 (0.22–2.29)	0.567		
Age-adjusted Charlson comorbidity index	1.16 (1.06–1.27)	**0.002**		
Prior antifungal therapy	1.37 (0.73–2.56)	0.324		
Prior azoles	1.68 (0.78–3.62)	0.182		
Prior polyenes	1.30 (0.56–2.99)	0.538		
Prior echinocandins	1.36 (0.65–2.81)	0.412		
Prior antibiotic therapy	1.18 (0.64–2.16)	0.603		
Prior chemotherapy	1.37 (0.70–2.70)	0.360		
Prior major surgery	1.32 (0.73–2.40)	0.356		
Probable invasive pulmonary mould disease according to EORTC/MSGERC definitions	1.04 (0.58–1.86)	0.888		
Probable invasive pulmonary aspergillosis according to FUNDICU definitions	1.22 (0.67–2.20)	0.515		
Antifungal prophylaxis with mould-active agents	0.72 (0.26–2.01)	0.533		
Days from ICU admission to isavuconazole initiation	1.00 (0.99–1.01)	0.937		
SOFA score	1.15 (1.05–1.25)	**0.002**	1.17 (1.07–1.28)	**<0.001**
Presence of septic shock	2.19 (1.21–3.98)	**0.010**		
Invasive mechanical ventilation	2.14 (1.05–4.33)	**0.036**		
Presence of AKI	1.43 (0.81–2.54)	0.221		
CRRT	1.71 (0.90–3.24)	0.102		
ECMO	0.39 (0.05–2.86)	0.357		
Concomitant candidaemia	0.53 (0.13–2.19)	0.379		
Concomitant bacteraemia	0.92 (0.49–1.73)	0.797		
Concomitant CABP, HABP or VABP	1.56 (0.88–2.77)	0.130		
Additional antifungal therapy for fungal infections other than IA and mucormycosis	1.13 (0.60–2.13)	0.694		
Concomitant antibiotic therapy	1.57 (0.56–4.38)	0.388		
Combination antifungal therapy	0.44 (0.16–1.24)	0.122		
Probable invasive pulmonary mould disease (versus proven IA/mucormycosis as ref.)	2.44 (0.59–10.06)	0.218		

Analyses conducted after multiple imputation (see study methods). Bold values are significant at the selected level of significance ($\alpha = 0.05$).
AKI, acute kidney injury; CI; confidence interval; CABP, community-acquired bacterial pneumonia; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; EORTC, European Organisation for Research and Treatment of Cancer; FUNDICU, invasive FUNgal Diseases in adult patients in Intensive Care Unit; HABP, hospital-acquired bacterial pneumonia; NYHA, New York Heart Association; LTCF, long-term care facility; MSGERC, Mycoses Study Group Education and Research Consortium; SOT, solid organ transplantation; VABP, ventilator-associated bacterial pneumonia.
[a]Only results of the final multivariable model (Model C) after stepwise backward selection are presented. Variables included in the initial multivariable model were prior hospitalization, chronic kidney disease, age-adjusted Charlson comorbidity index, SOFA score, presence of septic shock and invasive mechanical ventilation.
[b]No patients with admission from LTCF among those with proven or probable disease.

phase conditions possibly increasing the risk of unfavourable prognosis, as factually supported by the association of both high SOFA score and concomitant pneumonia with 30-day mortality in our study (the unfavourable prognostic effect of a baseline high SOFA score also persisted after 90 days, when it became paired by that of prior hospitalization, the latter possibly reflecting, in our opinion, the unfavourable prognostic effect of chronic conditions, that may result in more episodes of hospitalization over time). In this context, a favourable prognostic impact of isavuconazole cannot be excluded, in line with the preliminary

findings by Volpi *et al.*,[34] although this hypothesis should by weighed with due caution considering the indirect comparison with previous literature, as well as the lack of comparative groups in our study, and deserves further investigation.

Besides the lack of comparative treatments, which is a limitation in terms of our secondary analysis but not for our primary objective of describing the use isavuconazole in ICU patients, the present study has other limitations related to secondary prognostic assessments. The first is the lack of comparison of 30-day and 90-day mortality between patients with proven and probable disease, reflecting the very low number of patients with proven disease in our cohort that precluded any possible reliable comparison. The second, again relying on the small size of the pertinent subgroup (i.e. patients who underwent isavuconazole TDM), is the lack of assessment of any possible unfavourable prognostic effect of low isavuconazole blood levels, hypothesized on the previously reported higher frequency of levels < 2 mg/L in ICU patients compared to other populations, although it should be acknowledged that the existence of such an unfavourable prognostic impact still remains controversial.[38–47] In patients undergoing TDM in our cohort, changes in the dosage of isavuconazole were registered very rarely, possibly reflecting, on the one hand, the need for further evidence before supporting standardized dosage increases in case of low levels and, on the other hand, the infrequent, albeit possible, occurrence of toxicity in case of higher-than-normal blood levels.[46,47] This latter consideration is also in line with the low number of drug-related AEs reported in our cohort, as well as with the lower potential for drug interactions of isavuconazole compared to other antifungals of the same class.[48–50] In this context, it should also be acknowledged that the small denominator of patients with more than one determination of blood levels available precluded reliable analyses of the within-subject variability of levels and of any possible prognostic impact of the persistence over time of either low or high blood levels, which deserve further investigation. Finally, the relatively short median length of therapy for invasive IA or mucormycosis recorded in our cohort is possibly related to the loss to follow-up of improved patients who continued therapy after discharge, who were excluded from the median length calculation in the absence of the actual time of isavuconazole discontinuation.

In conclusion, our study demonstrated diverse patterns of isavuconazole use in terms of baseline host factors and disease characteristics in a large cohort of critically ill adult patients and that the drug was generally well tolerated. Cumulative mortality, assessed in patients with proven or probable disease according to the EORTC/MSGERC and FUNDICU definitions, was lower than many previous estimates in critically ill patients with IA and could serve as a basis for future standardized comparisons.

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Author contributions

Conceptualization, D.R.G. and M.Bas.; methodology, D.R.G., M.Mu. and A.S.; formal analysis, M.Mu.; data curation, C.B., M.Bav., R.S., V.D.P., C.A., J.A., E.A., E.B.V., N.B., E.B., B.C., A.Cal., M.Cas., A.Cat., S.C., F.C., G.D.P., F.G.D.R., V.D.B., F.D.P., C.F., F.F., E.F., N.G., M.G., S.G., I.M., A.M., M.Ma., M.C.M., M.Mer., M.Mes, C.M., C.O., R.P., S.P., E.P., M.Ric., M.Rin., A.R., M.S., V.S., F.S., F.S.S., N.S., C.T., G.T., L.M., F.P., F.B., M.Mi., L.B., C.R., N.P., D.B., M.G., E.C., A.M. and A.V.; writing—original draft preparation, D.R.G.; writing—review and editing, D.R.G., M.Mu., C.B., M.Bav., R.S., V.D.P., A.S., C.A., J.A., E.A., E.B.V., N.B., E.B., B.C., A.Cal., M.Cas., A.Cat., S.C., F.C., G.D.P., F.G.D.R., V.D.B., F.D.P., C.F., F.F., E.F., N.G., M.G., S.G., I.M., A.M., M.Ma., M.C.M., M.Mer., M.Mes, C.M., C.O., R.P., S.P., E.P., M.Ric., M.Rin., A.R., M.S., V.S., F.S., F.S.S., N.S., C.T., G.T., L.M., F.P., F.B., M.Mi., L.B., C.R., N.P., D.B., M.G., E.C., A.M., A.V. and M.Bas.; and supervision, D.R.G., A.M., M.Mi., M.G., N.P., A.V., A.S. and M.Bas. All authors have read and agreed to the submitted version of the manuscript.

Data availability

The data presented in this study will be available from the corresponding author on reasonable request and provided all regulatory and privacy requirements are fulfilled.

Supplementary data

Supplementary Figures S1 and S2 and Tables S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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