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Do high MICs predict the outcome in invasive fusariosis?

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Background: Invasive fusariosis (IF) affects mostly severely immunocompromised hosts and is associated with poor outcome. Since *Fusarium* species exhibit high MICs for most antifungal agents, this could explain the poor prognosis. However, a clear-cut correlation between MIC and outcome has not been established.

Objective: To evaluate the correlation between MIC and outcome (6 week death rate) in patients with IF.

Methods: We performed a multicentre retrospective study of patients with IF who received treatment and had MIC levels determined by EUCAST or CLSI for the drug(s) used during treatment. We compared the MIC_{50} and MIC distribution among survivors and patients who died within 6 weeks from the diagnosis of IF.

Results: Among 88 patients with IF, 74 had haematological diseases. Primary treatment was monotherapy in 52 patients (voriconazole in 27) and combination therapy in 36 patients (liposomal amphotericin B +

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voriconazole in 23). The MIC_{50} and range for the five most frequent agents tested were: voriconazole 8 mg/L (range 0.5–64), amphotericin B 2 mg/L (range 0.25–64), posaconazole 16 mg/L (range 0.5–64), itraconazole 32 mg/L (range 4–64), and isavuconazole 32 mg/L (range 8–64). There was no difference in MIC_{50} and MIC distribution among survivors and patients who died. By contrast, persistent neutropenia and receipt of corticosteroids were strong predictors of 6 week mortality.

Conclusions: Our study did not show any correlation between MIC and mortality at 6 weeks in patients with IF.

Introduction

Invasive fusariosis is an invasive fungal disease that affects mostly severely immunocompromised hosts, such as patients with acute leukaemia and allogeneic haematopoietic cell transplant (HCT) recipients.[1] Various *Fusarium* species may cause invasive disease, but most cases are caused by either *Fusarium solani* species complex (FSSC, ∼50%), *Fusarium oxysporum* species complex (FOSC, ∼20%), or *Fusarium fujikuroi* species complex (FFSC).[2] The disease has a poor prognosis, with a 90 day survival rate of 45% only.[3] The outcome is largely dependent on immune reconstitution, especially recovery of neutropenia,[4] but poor outcomes are also thought to be due to elevated *in vitro* MICs exhibited by most *Fusarium* species for most antifungal agents.[5] However, a clear-cut correlation between MIC and outcome has not been established. Indeed, *in vitro* data show that most *Fusarium* species exhibit high MICs for voriconazole, yet this agent seems to be as effective as lipid amphotericin B.[3,6] Despite these discrepancies, antifungal susceptibility tests are recommended to guide the choice of antifungal therapy,[7] but the level of evidence is weak, reflecting the lack of clinical data. In this study, we evaluated the correlation between MIC and outcome in patients with invasive fusariosis.

Patients and methods

This was a multicentre retrospective study. We collected data from patients with invasive fusariosis treated in 22 centres from seven countries (Austria, Brazil, Chile, Italy, the Netherlands, Spain and the USA). This study was approved by the Ethics Committees of participating centres. Patients were included in the study if they: (i) had a diagnosis of invasive fusariosis; (ii) received treatment with one or more antifungal agents; (iii) data on antifungal susceptibility testing for the drug(s) used in the treatment of invasive fusariosis, performed either according to EUCAST or CLSI were available; and (iv) information about the outcome (6 week mortality) was available. Cases of possible invasive fusariosis as per the revised European Organization for Treatment and Research of Cancer/Mycosis Study Group (EORTC/MSG)[8] criteria were excluded.

We built a database containing demographic information (gender and age at diagnosis of invasive fusariosis), underlying condition, clinical context in which the patient developed invasive fusariosis, presence and duration of neutropenia, receipt of corticosteroids, date of diagnosis, species causing infection, MIC, treatment (regimen, date of start and end of treatment), and the outcome (dead or alive) 6 weeks after the diagnosis of invasive fusariosis.

We classified fusariosis as either disseminated disease, fungaemia or localized disease (sinusitis, pneumonia, peritonitis, soft tissue infection). Disseminated invasive fusariosis was defined as involvement of >1 non-contiguous organs.[3] Cases of fungaemia were not defined as disseminated disease unless another organ systems were involved (e.g. skin, lung or sinuses). Neutropenia was defined as an absolute neutrophil count <500 cells/mm^3, and neutrophil recovery was defined as the absolute neutrophil count >500 cells/mm^3 in a patient with previous neutropenia.

In order to evaluate the correlation between MIC and outcome, we considered that a patient received one drug (e.g. voriconazole) if it had been given as primary monotherapy, or as salvage therapy after <5 days of treatment with another regimen. We compared the MIC_{50} for that agent among survivors and patients who died within 6 weeks from the diagnosis of invasive fusariosis. Then, we analysed patients who received combination therapy, and explored the association between MIC distribution and MIC_{50} for the two agents used in combination therapy and the outcome. The Mann–Whitney *U*-test was used to compare MIC_{50} among patients who survived and those who died. Categorical variables were compared using χ^2 test. We used the Kaplan–Meier method to evaluate time to death according to the underlying immunosuppressive state. *P* values <0.05 were considered statistically significant.

Results

We identified 88 patients, including 28 from Brazil, 22 from the USA, 19 from Italy, 11 from Spain, 4 from Austria, and 2 each from the Netherlands and Chile. The median age was 51.5 years (range 4–73), and 61 (69.3%) were males. As shown in Table 1, 74 (84.1%) had a haematological condition (including acute myeloid leukaemia in 37 patients). There were six patients with burn-associated invasive fusariosis, two with infected wounds, two solid organ transplant recipients (kidney and lung, $n = 1$ each), and four patients with lung ($n = 2$), liver ($n = 1$) or kidney ($n = 1$) failure.

Table 1. Characteristics of 88 patients with invasive fusariosis

Characteristic	No.
Age (years), median (range)	51.5 (4–73)
Gender, male:female	61:27
Scenario/underlying disease, *n* (%)	
haematological disease	74 (84.1)
acute myeloid leukaemia	37 (42.0)
acute lymphoid leukaemia	8 (9.1)
Non-Hodgkin's lymphoma	8 (9.1)
multiple myeloma	6 (6.8)
aplastic anaemia	5 (5.7)
other[a]	10 (11.4)
wound/burn	8 (9.1)
burn	6 (6.8)
wound	2 (2.3)
chronic organ failure[b]	4 (4.5)
solid organ transplantation[c]	2 (2.3)

[a]Other haematological diseases: chronic myeloid leukaemia, myelodysplasia, chronic lymphoid leukaemia, myelofibrosis (n=2 each), haemophilia, dendritic cell leukaemia ($n = 1$ each).
[b]Lung ($n = 2$), liver and kidney ($n = 1$ each).
[c]Lung and kidney ($n = 1$ each).

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Among the 74 patients with haematological disease, invasive fusariosis occurred in the context of chemotherapy in 46 (62.2%), post-transplant in 25 (33.8%), following immunosuppressive therapy for aplastic anaemia in two cases, and one case of fungaemia in a patient with haemophilia. As shown in Table 2, disseminated disease or fungaemia occurred in 63 patients, all cases in patients with haematological diseases. Soft tissue infection occurred in 10 patients. The other clinical presentations were pneumonia and sinusitis (seven patients each) and peritonitis (one patient).

Neutropenia was present in 65 patients at diagnosis of invasive fusariosis, and neutrophil recovery occurred during treatment in 37 of 65 patients (56.9%). A total of 39 patients (44.3%) were receiving corticosteroids at diagnosis of fusariosis (37 with haematological diseases and two solid organ transplant recipients).

Species distribution of *Fusarium* isolates in the 88 patients was as follows: FSSC ($n=40$, 45.4%), FOSC ($n=9$, 10.2%), FFSC ($n=5$, 5.7%) and *Fusarium dimerum* species complex ($n=2$). In 32 patients species was not identified. Antifungal susceptibility tests were performed according to CLSI in 45 patients and EUCAST in the remaining 43 patients. The most frequent antifungal agent tested was voriconazole (87 of 88 patients), followed by amphotericin B ($n=86$), posaconazole ($n=82$) and itraconazole ($n=31$). Other agents tested were isavuconazole ($n=19$), caspofungin ($n=12$), micafungin ($n=8$), anidulafungin and terbinafine ($n=4$ each) and olorofim ($n=1$).

Considering that two methods of antifungal susceptibility were employed, we compared the MIC_{50} of amphotericin B and voriconazole against the two most frequent species (FSSC and FOSC), tested with CLSI and EUCAST. Among FSSC isolates, the MIC_{50} using CLSI and EUCAST was 2 mg/L (range 0.5–64) and 2 mg/L (range 0.5–64), respectively, for amphotericin B, and 4 mg/L (range 1–32) and 8 mg/L (range 0.5–64), respectively, for voriconazole. Among FOSC isolates, the MIC_{50} using CLSI and EUCAST was 1.5 mg/L (range 1–4) and 2 mg/L (range 1–2) for amphotericin B, and 4 mg/L (range 2–8) and 8 mg/L (range 1–16) for voriconazole. None of the comparisons was statistically significant.

The MIC_{50} and range for the five most frequent agents tested were as follows: voriconazole 8 mg/L (range 0.5–64), amphotericin B 2 mg/L (range 0.25–64), posaconazole 16 mg/L (range 0.5–64), itraconazole 32 mg/L (range 4–64) and isavuconazole 32 mg/L (range 8–64). Table 3 shows MIC values of these antifungal agents according to the species causing infection. Overall, FSSC exhibited higher MICs compared with FOSC and FFSC.

Primary treatment for invasive fusariosis was monotherapy in 52 patients (59.1%) and combination therapy in 36 patients (two drugs in 34 patients and three drugs in 2 patients). The treatment was started at a median of zero days from diagnosis of invasive fusariosis (range −16 to 15). As shown in Table 4, the most frequent regimen was monotherapy with voriconazole (27 patients, 30.7%), followed by liposomal amphotericin B + voriconazole (23 patients, 26.1%) and liposomal amphotericin B alone (16 patients, 18.2%). The antifungal regimen was changed in 30 patients (34.1%), at a median of 10 days from the start of treatment (range 1–64). Reasons for change in the primary regimen were worsening clinical conditions in 17 patients and de-escalation from combination or IV therapy to oral therapy in 13 patients (voriconazole in 10 patients, posaconazole in two patients and terbinafine in one patient).

The overall 6 week mortality rate was 33.0%, being 36.5% in patients with haematological diseases, 16.7% in patients with other immunosuppressive conditions (solid organ transplantation and organ failure) and 12.5% in patients with soft tissue infection after trauma or burn (Figure 1). The 6 week mortality by species was 40% (16 of 40) in cases caused by FSSC, 33% (3 of 9) with FOSC and 60% (3 of 5) with FFSC ($P=0.61$).

To assess MIC and outcome, we separately analysed patients with haematological diseases and patients with other conditions. Among 22 patients with haematological diseases who received treatment with voriconazole, the 6 week death rate was 36.4%. As shown in Table 5, the MIC_{50} of voriconazole was 4 mg/L (range 1–32) in survivors and 8 mg/L (range 1–32) in patients who died ($P=0.68$). Twenty-one haematological patients received amphotericin B as primary therapy. The 6 week death rate among these patients was 38.1%. The MIC_{50} was 2 mg/L (range 0.5–16) in survivors and 2 mg/L (range 1–32) in patients who died ($P=0.66$). Among 29 patients with haematological diseases who received a

Table 3. MIC of five antifungal agents according to the species causing invasive fusariosis

	MIC_{50}, mg/L (range)		
	FSSC	FOSC	FFSC
Amphotericin B	2 (0.5–64)	1 (2–4)	1 (4–16)
Voriconazole	8 (0.5–64)	4 (1–16)	4 (1–16)
Posaconazole	32 (0.5–64)	4 (2–16)	16 (1–32)
Itraconazole	48 (8–64)	16	40 (16–64)
Isavuconazole	48 (8–64)	8 (8–16)	40 (16–64)

FSSC, *Fusarium solani* species complex; FOSC, *Fusarium oxysporum* species complex; FFSC, *Fusarium fujikuroi* species complex.

Table 2. Clinical form of invasive fusariosis according to the scenario

Clinical form	Haematology, $N=74$ (%)	Solid organ transplantation, $N=2$ (%)	Wound/burn, $N=8$ (%)	Chronic organ failure, $N=4$ (%)
Disseminated	50 (67.6)	–	–	–
Fungaemia	13 (17.6)	–	–	–
Soft tissue infection	–	1 (50)	8 (100)	1 (25)
Pneumonia	4 (5.4)	1 (50)	–	2 (50)
Sinusitis	7 (9.4)	–	–	–
Peritonitis	–	–	–	1 (25)

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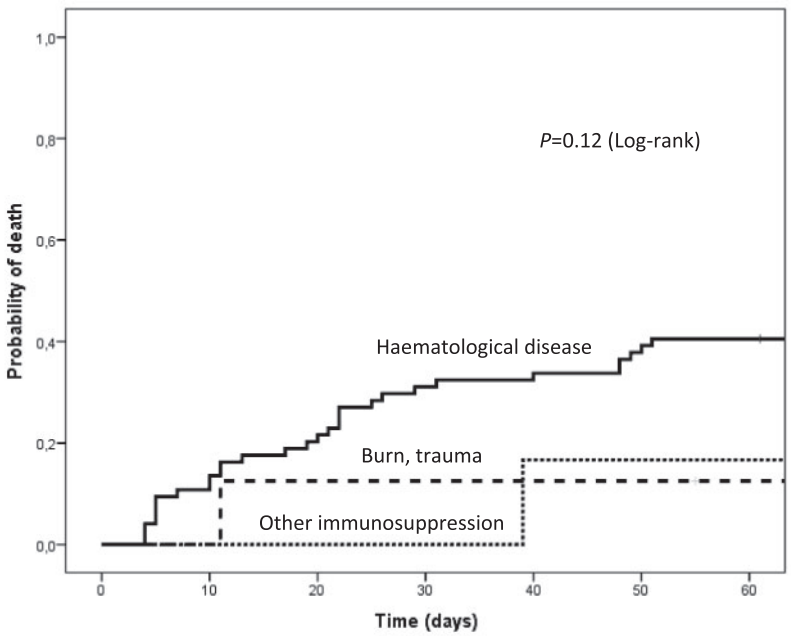
Table 4. Primary antifungal therapy and 6 week death rate in 88 patients with invasive fusariosis

Treatment	No. (%)	6 week death rate (%)
Monotherapy	52 (59.1)	32.7
voriconazole	27 (30.7)	29.6
liposomal amphotericin B	16 (18.2)	31.3
deoxycholate amphotericin B	5 (5.7)	60.0
amphotericin B lipid complex	3 (3.4)	33.3
posaconazole	1 (1.1)	–
Combination therapy	36 (40.9)	33.3
liposomal amphotericin B + voriconazole	23 (26.1)	21.7
deoxycholate amphotericin B + voriconazole	9 (10.2)	55.6
other[a]	4 (4.5)	–

[a]Other combination therapy: liposomal amphotericin B + voriconazole + terbinafine ($n = 2$), isavuconazole + micafungin and amphotericin B lipid complex + voriconazole ($n = 1$ each).



Haematological disease	74	65	54	44	34	24	14
Other immunosuppression	6	6	6	6	5	5	5
Burn, trauma	8	7	7	7	7	7	7

Figure 1. Kaplan–Meier curve for time to death in 88 patients with invasive fusariosis according to the underlying immunosuppressive state.

combination of amphotericin B and voriconazole, the 6 week death rate was 34.5%. The MIC_{50} of amphotericin B among survivors and patients who died was 2 mg/L (range 0.25–64) and 2 mg/L (range 0.5–16), respectively ($P = 1.0$). The MIC_{50} of voriconazole was 8 mg/L (range 0.5–64) among survivors and 4 mg/L (range 1–32) among patients who died ($P = 1.0$).

We further analysed the relationship between neutrophil recovery, receipt of corticosteroids and outcome in haematological patients. Neutrophil recovery occurred in 37 of 65 patients with neutropenia (56.9%). The 6 week death rate was 64.3% in patients with persistent neutropenia and 13.5% in patients who recovered from neutropenia ($P < 0.001$). Similarly, patients receiving corticosteroids had a higher 6 week death rate compared with those not on corticosteroids (48.6% versus 24.3%, respectively, $P = 0.03$).

Among the 14 patients with non-haematological conditions, only two patients died, including one patient with soft tissue infection after burn and a patient with chronic liver disease and peritonitis. The first patient was treated with a combination of liposomal amphotericin B and voriconazole and the isolate exhibited MIC for amphotericin B and voriconazole of 1 and 4 mg/L, respectively. The other patient was treated with liposomal amphotericin B, with an MIC of 2 mg/L. The other 12 patients were treated with

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Table 5. Distribution of MIC of voriconazole and amphotericin B in 72[a] haematological patients with invasive fusariosis

		No. of isolates with MIC (mg/L)									
Primary therapy	No.	0.25	0.5	1	2	4	8	16	32	64	MIC_{50}
Voriconazole	22										
survival	14	0	0	2	3	3	3	2	1	0	4
death	8	0	0	2	0	1	2	2	1	0	8
Amphotericin B	21										
survival	13	0	1	3	4	4	0	1	0	0	2
death	8	0	1	2	3	1	0	0	1	0	2
Amphotericin B + voriconazole	29										
amphotericin B											
survival	19	2	2	3	8	3	0	0	0	1	2
death	10	0	2	1	5	1	0	1	0	0	2
voriconazole											
survival	19	0	1	2	3	2	6	0	3	2	8
death	10	0	0	1	4	0	2	2	1	0	4

[a]One patient with haematological disease received posaconazole and one received isavuconazole + micafungin.

voriconazole ($n = 7$) or voriconazole + liposomal amphotericin B ($n = 5$). The MIC_{50} for *Fusarium* isolates for amphotericin B and voriconazole in these 12 patients was 2 mg/L (range 1–16) and 16 mg/L (range 1–32), respectively.

Discussion

In this study, we did not find any correlation between MIC and death at 6 weeks for patients with invasive fusariosis, as shown by similar MIC_{50} and MIC distributions among haematological patients who survived and those who died, and high MICs in patients with non-haematological diseases who survived. By contrast, we found that host factors (persistent neutropenia and receipt of corticosteroids) were strong predictors of mortality at 6 weeks.

In this study, patients with invasive fusariosis comprised three groups: patients with haematological malignancies with neutropenia and receipt of corticosteroids, the majority of whom presented with either fungaemia or disseminated disease, patients with other immunosuppressive conditions such as solid organ transplantation and organ failure with single organ involvement (pneumonia, sinusitis, peritonitis, soft tissue infection), and non-immunocompromised patients with soft tissue infection after trauma or burn.

Interestingly, we found that voriconazole was the most frequent agent used for the treatment of invasive fusariosis, either alone or in combination with amphotericin B. This is perhaps surprising considering that the MIC_{50} of voriconazole was 8 mg/L, suggesting that clinicians did not take MIC results in consideration when they chose the drug for primary therapy. The preference for voriconazole for the treatment of invasive fusariosis may be due to the fact that the major guideline groups recommend this as first-line therapy.[9]

In our study, about 50% of isolates had MIC determination performed with either CLSI or EUCAST. A study comparing these two methods in 20 clinical isolates of *Fusarium* species showed 100% agreement with ±1 dilution for amphotericin B, and 95% for voriconazole.[10] We compared the MICs of amphotericin B and voriconazole against FSSC and FOSC with the two methods, and did not find significant differences. These data indicate that it is reasonable to aggregate MIC data using the two methods.

The MIC distribution observed in our study is consistent with other reports,[11,12] with higher MICs for azoles compared with amphotericin B, and higher MICs with FSSC isolates compared with other species. While clinical breakpoints for *Fusarium* have not been established, epidemiological cut-off values for the most frequent species were established in a multicentre analysis of 1150 isolates.[5] While no studies have evaluated the clinical relevance of these epidemiological breakpoints, an *in vivo* murine model of invasive fusariosis did not show any correlation between these breakpoints and the outcome.[13]

In our analysis of the relationship between MIC and outcome in patients with haematological diseases, we found that the MIC_{50} of voriconazole and amphotericin B in patients who died and patients who survived was very similar, with differences that did not go beyond one dilution. Likewise, the MIC distributions according to the outcome were similar. These results were consistent across different *Fusarium* species, in neutropenic and non-neutropenic patients (data not shown), as well as in patients who received monotherapy versus combination therapy. For example, among patients treated with voriconazole monotherapy, the proportion of patients with MIC ≥16 mg/L was 21.4% in survivors and 37.5% in patients who died (Table 5). In patients receiving amphotericin B monotherapy, the proportion of survivors and patients who died with MIC >2 mg/L was 38.5% and 25%, respectively.

Although there was a lack of correlation between MIC and outcome, we found a strong relationship between neutrophil

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recovery, receipt of corticosteroids and 6 week survival. These host factors were identified as independent predictors of outcome in a study evaluating 84 haematological patients with fusariosis. The 90 day actuarial survival was zero in patients with persistent neutropenia and receipt of corticosteroids, 4% in patients with persistent neutropenia and no corticosteroid use, 30% in patients receiving corticosteroids with neutrophil recovery, and 67% in patients with neither of these factors.[4] Recently, an analysis of prognostic factors in a cohort of 233 cases of invasive fusariosis showed the same two variables as independent predictors of the outcome.[3]

Although the number of patients with non-haematological conditions was small, with only two deaths among 14 patients, the MIC values in the 12 patients who survived do not suggest a correlation between MIC and outcome.

Due to its retrospective nature, this study has some important limitations. First, despite a great effort to gather as many cases as possible, one limitation of the study is the relatively small sample size, especially in patients with non-haematological conditions. Still, invasive fusariosis is a rare entity so compiling a large number of cases for such a study would be difficult. Second, 32 of the 88 cases did not have species identification as not all centres routinely perform speciation. Third, some variables that could have an impact on the outcome, such as status of the underlying malignancy and cumulative dose of corticosteroids, were not available. Fourth, the analysis of the correlation between MIC and outcome in patients receiving combination therapy did not take into account possible interactions between the drugs. Fifth, we did not have information about voriconazole serum levels in patients treated with this drug. Finally, although EUCAST and CLSI seem to have good agreement for MIC determination, the best scenario would be if all MICs had been determined using one of the two methods, preferably in only one reference laboratory.

Despite these limitations, our study has important clinical and experimental implications. First, while MIC determination may be useful for epidemiological purposes, the results of this study show that MIC should not guide clinicians in choosing which antifungal agent to use to treat invasive fusariosis. Likewise, some experts recommend the use of combination therapy with the justification that since most *Fusarium* species exhibit high MICs for voriconazole, it would be safer to start treatment with amphotericin B and an azole (usually voriconazole). The data presented in this study do not support such an approach as the mortality rate at 6 weeks was similar between those treated with voriconazole and amphotericin B monotherapy and combination therapy with voriconazole plus amphotericin B. Indeed, voriconazole monotherapy was the most frequent regimen, even in neutropenic patients. From the experimental standpoint, during the development of new antifungal drugs, a high MIC for *Fusarium* species should not be strongly taken into account to discard the drug as potentially ineffective for the treatment of invasive fusariosis. If these assumptions have been established, voriconazole would never be an option for the treatment of invasive fusariosis. Finally, our study reinforces the great importance of recovery of host defences in the prognosis of invasive fusariosis.

In conclusion, our study did not show any correlation between MIC and mortality at 6 weeks in patients with invasive fusariosis, indicating that MIC should not be used to choose the first-line therapy.

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Transparency declarations

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References

1 Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. *Clin Microbiol Rev* 2007; **20**: 695–704.

2 van Diepeningen AD, Al-Hatmi AMS, Brankovics B *et al*. Taxonomy and clinical spectra of Fusarium species: where do we stand in 2014? *Curr Clin Micro Rpt* 2014; **1**: 10–8.

3 Nucci M, Marr KA, Vehreschild MJ *et al*. Improvement in the outcome of invasive fusariosis in the last decade. *Clin Microbiol Infect* 2014; **20**: 580–5.

4 Nucci M, Anaissie EJ, Queiroz-Telles F *et al*. Outcome predictors of 84 patients with hematologic malignancies and Fusarium infection. *Cancer* 2003; **98**: 315–9.

5 Espinel-Ingroff A, Colombo AL, Cordoba S *et al*. International Evaluation of MIC Distributions and Epidemiological Cutoff Value (ECV) definitions for fusarium species identified by molecular methods for the CLSI broth microdilution method. *Antimicrob Agents Chemother* 2016; **60**: 1079–84.

6 Lortholary O, Obenga G, Biswas P *et al*. International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. *Antimicrob Agents Chemother* 2010; **54**: 4446–50.

7 Tortorano AM, Richardson M, Roilides E *et al*. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. *Clin Microbiol Infect* 2014; **20** Suppl 3: 27–46.

8 Donnelly JP, Chen SC, Kauffman CA *et al*. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis* 2020; **71**: 1367–76.

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9 Jenks JD, Mehta SR, Hoenigl M. Broad spectrum triazoles for invasive mould infections in adults: which drug and when? *Med Mycol* 2019; **57**: S168–78.

10 Al-Hatmi AM, Normand AC, Ranque S *et al*. Comparative evaluation of Etest, EUCAST, and CLSI methods for amphotericin B, voriconazole, and posaconazole against clinically relevant Fusarium species. *Antimicrob Agents Chemother* 2016; **61**: e01671–16.

11 Taj-Aldeen SJ, Salah H, Al-Hatmi AM *et al*. In vitro resistance of clinical Fusarium species to amphotericin B and voriconazole using the EUCAST antifungal susceptibility method. *Diagn Microbiol Infect Dis* 2016; **85**: 438–43.

12 Tortorano AM, Prigitano A, Dho G *et al*. Species distribution and in vitro antifungal susceptibility patterns of 75 clinical isolates of Fusarium spp. from northern Italy. *Antimicrob Agents Chemother* 2008; **52**: 2683–5.

13 Navarro-Rodriguez P, Guevara-Suarez M, Paredes K *et al*. Lack of correlation of ECV and outcome in an in vivo murine model of systemic fusariosis. *Diagn Microbiol Infect Dis* 2018; **92**: 124–6.

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