Prior exposure to voriconazole does not change the frequency of infections with mixed *Aspergillus* and *Mucorales*, versus *Mucorales*

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Abstract

Objective: To assess the incidence of invasive mucormycosis (IM) with or without other invasive filamentous fungal infections (IFI), stratified by at-risk groups, in the era of voriconazole use and compare it to patients who developed IM prior to voriconazole availability.

Methods: We reviewed all cases of IM seen at Mayo Clinic from 1995 to 2011. Cases of IM were categorized as "mixed" if one or more fungi were isolated or identified from the same specimen in which Mucorales was found. We divided these into 2 eras (E): E1 from 1995-2003 before voriconazole, E2 from 2004-2011 when voriconazole was available. We defined 4 at-risk groups: solid organ transplant patients (SOT); stem cell transplant patients (SCT); non-transplant patients with hematologic or oncologic disorders (H/O); non-transplant, non-H/O patients. We abstracted and compared clinical, mycologic, treatment, and outcome data and compared these between eras and between pure IM and mixed IFIs groups using standard statistical tests (Student`s t-test, chi square test, log-rank test.)

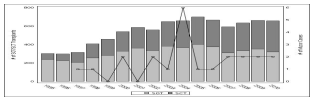
Results: Total of 101 cases (79 proven, 22 probable) were recorded. 30 cases were in E1 and 71 cases in E2. No significant difference was noted in age (p=0.828), gender (p=0.471), or rates of pure IM vs. mixed IFIs (p=0.115), between E1 and E2. When combining the frequency across eras, isolated cases of Mucorales were (n=75), Mucorales in combination with *Aspergillus* spp. (n=23), and Mucorales in combination with *Alternaria* (n=3). Between E1 and E2, there were significant differences in prior use of any antifungal agent (50% vs. 74%, p=0.0170); and in the spectrum of prior antifungal used (yeast only, 80% vs. 25%; molds but not Mucorales, 7% vs. 73%; molds including Mucorales, 13% vs. 2%; p<. 001). Between the pure vs. mixed group, no significant difference was seen in the rates of neutropenia (p value 0.444), or of surgical debridement (0.208). When comparing 90-day survival curves for pure Mucorales versus mixed IFIs (Mucorales and *Aspergillus* or *Alternaria*), there was a trend towards better survival in the mixed group although the result was not statistically significant.

Conclusions: A quarter of the patients with IM had co-infection with *Aspergillus* or *Alternaria*. There were no significant differences in the rate of surgical debridement and survival between patients with pure IM and those with mixed IFI.

Methods

- All IM cases at Mayo Clinic from 1995-2011 were reviewed and divided into 2 time blocks, E1 (1995-2003), E2 (2004-2011)
- Cases were identified through search of microbiology and histopathology databases and classified using European Organization for Research and Treatment of Cancer/ Mycoses Study group criteria (EORTC / MSG). Criteria was modified to include cases of diabetes mellitus
- Only Proven and Probable cases were included in the final analysis
- 4 At-Risk groups were defined: Solid organ transplant (SOT) recipients, Stem cell transplant (SCT) recipients, patients with hematologic or oncologic (H/O) disorders, non hematological (Non H/O) patients
- We compared clinical and microbiologic characteristics of patients and analyzed treatment and outcome data across 4 at-risk groups

Figure 1



Documented cases of SOT, SCT & Mucorales at Mayo Clinic 1995-2010

Table 1 : Comparison of cases of pure Mucorales and mixed IFIs

Variable	1995-2003 (n=30)	2004-2011 (n=71)	P-value
Mucorales Species identified			**0.115***
Mucorales	24 (80%)	51 (72%)	
Mucorales + *Aspergillus*	4 (13%)	19 (27%)	
Mucorales + Other	2 (7%)	1 (1%)	

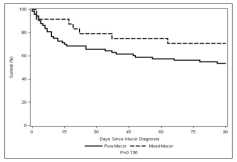
Table 2: Results

Variable	Pure (n=75)	Mixed (n=26)	P-value
Age (years) at time of Mucorales diagnosis	52.2±16.2	53.0±14.0	0.828
Sex			0.471
Female	43 / 75 (57%)	17 / 26 (65%)	
Male	32 / 75 (43%)	9 / 26 (35%)	
At-Risk Group			0.454
SOT	11 / 75 (15%)	6 / 26 (23%)	
SCT	12 / 75 (16%)	6 / 26 (23%)	
Heme-Onc	39 / 75 (52%)	9 / 26 (35%)	
Other	13 / 75 (17%)	5 / 26 (19%)	
Site			0.129
MCR	59 / 75 (79%)	16 / 26 (62%)	
MCA	5 / 75 (7%)	5 / 26 (19%)	
MCF	11 / 75 (15%)	5 / 26 (19%)	
Year of onset of Mucorales			**0.391**
1995-2003	24 / 75 (32%)	6 / 26 (23%)	
2004-2011	51 / 75 (68%)	20 / 26 (77%)	
Strength of IM diagnosis			0.066
Definite	62 / 75 (83%)	17 / 26 (65%)	
Probable	13 / 75 (17%)	9 / 26 (35%)	

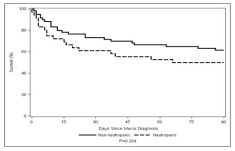
Variable	Pure (n=75)	Mixed(n=26)	P-value
Mucorales Site			0.166
Rhino-Orbital Cerebral	17 / 75 (23%)	5 /26 (19%)	
Pulmonary	29 / 75 (39%)	16 /26 (62%)	
Abdominal/ Other	17 / 75 (23%)	4 / 26 (15%)	
Multiple sites	12 /75 (16%)	1 / 26 (4%)	
Prior Antifungal Exposure	47 / 75 (63%)	23 /26 (88%)	0.014
Antifungal Exposure			0.745*
Non active against IFI	19 / 47 (40%)	7 / 23 (30%)	
Active against IFI	26 / 47 (55%)	15 /23 (65%)	
Active against all IFI	2 / 47 (4%)	1 / 23 (4%)	
Surgical debridement	48 / 75 (64%)	13 /26 (50%)	0.208
Neutropenia at onset of Mucorales	29 / 74 (39%)	8 / 26 (31%)	0.444
Post Diagnosis (at 14 day follow up)			0.566*
0-6 days of therapy	11 / 52 (21%)	7 / 22 (32%)	
AMB alone	27 / 52 (52%)	9 / 22 (41%)	
AMB in combination with CASPO and/ or POSA	13 / 52 (25%)	5 / 22 (23%)	
CASPO/POSA/VORI combinations without AMB	1 / 52 (2%)	1 / 22 (5%)	
Deaths,# events			
At 30-day follow up	25 (34%)	5 (21%)	0.207
At 90-day follow up	34 (47%)	7 (29%)	0.136
At 1 year follow up	43 (59%)	12 (51%)	0.295

P- values derived from Student`s t-test or chi square tests, unless noted otherwise
*p-value from Fischers exact test due to sparse data
+rates of death (%) estimated using Kaplan-Meier method and compared between groups using log-rank test

Figure 2



90-day survival for pure Mucorales vs. mixed mold infections



90-day survival for neutropenic vs. non neutropenic patients.

Conclusions

- A quarter of the patients with IM had co-infection with *Aspergillus* or *Alternaria*.
- There were no significant differences in the rate of surgical debridement and survival between patients with pure IM and those with mixed IFI.

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