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A Spanish National Survey on strategies for management of invasive fungal infection and guidelines application in high risk onco-hematological patients

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INTRODUCTION

- Invasive mold infections have increased in recent decades, and those caused by *Aspergillus fumigatus* are the most common. The mortality rate of these infections is very high and is mainly determined by patient risk factors; however, other issues, such as the infection being caused by a resistant strain, can also affect the patient outcome[1].
- The use of antifungals in prophylaxis and the appearance of azole-resistant Aspergillus fumigatus have conditioned an epidemiological change that, together with the interactions of targeted therapies, has modified the management strategies of onco-hematological patients with invasive fungal infections (IFI)[1-2].

OBJECTIVE(S)

- To know the strategies of clinicians in the management of IFI in onco-hematological patients and the role of guidelines and recommendations in decision making.

METHOD(S)

- Cross-sectional multicenter survey with hematology or infectious diseases specialists, belonging to Spanish hospitals and experienced in treating IFI. Data collection was carried out through an electronic platform in February 2022. The survey questionnaire consisted of 12 questions. Each question had 4 closed answers and in most of them multiple answers were possible (1,2,5-7,12) (Table 1).

RESULT(S)

- Fifty-five experts from a total of 31 hospitals completed the survey. Thirteen out of 17 Spanish regions participated on the survey. Sixty-four percent of the participants were hematologists, and the remaining 36% were infectious disease specialists. Almost 4/5 experts (78%) treated the adult population, compared to 22% who were specialists in the pediatric population. The average experience of the experts' participants were 21 years.
- **Based on the latest epidemiological studies,**
  - 63.6% of participants indicated that there has been an increase in *Aspergillus* resistance to azoles.
  - The possible coexistence of mixed infection (resistant/susceptible *Aspergillus*) was a concerned to 100% of experts.
  - For 74.5% of participants these resistances in onco-hematological patients are mainly of clinical origin, due to the routine use of prophylaxis.
- **In the case of suspected resistance in a patient being treated for aspergillosis**,
  - 82% of surveyed professionals would change the antifungal drug family to another broad-spectrum antifungal therapy (with one or two drugs).
- **When the percentage of resistance of *A. fumigatus* against an azole is ≥10%**
  - An 87% indicated that a change should be made in the choice of early treatment.
- **In case of persistent febrile neutropenia (5 days),**
  - 59% indicated that they would perform early treatment (even in presence of nonspecific or absence of lung infiltrates in CT-SCAN).
- **Regarding breakthrough IFI,**
  - 65% indicated an increase in the incidence of Mucorales and
  - 65% that proven IFI were usually resistant to previously administered antifungals.
- **For antifungals failing to reach levels during the first days and suspected invasive aspergillosis,**
  - the most appropriate strategy for 62% would be to associate it to an antifungal from another family.

RESULT(S)

- **Respect a possible interaction of targeted therapy drugs (midostaurin or venetoclax) with antifungal agents, as antifungal prophylaxis**
  - 40% would use broad-spectrum azoles
  - 38% would use echinocandins
- **In the case of using echinocandins as prophylaxis and development of suspected breakthrough IFI,**
  - 67% would administer liposomal amphotericin B.

Table 1. Survey and answers

Answer, n (%)	Sample (N=55)
1. The latest epidemiological studies on resistance to Aspergillus carried out in Spain imply…	
That we are facing an increase in Aspergillus resistance to azoles	35 (63.6)
The percentages are still too low to consider changing the diagnosis/treatment strategy	24 (43.6)
The need to conduct Aspergillus resistance studies on a routine basis	23 (41.8)
The possible coexistence of mixed infection (resistant/susceptible Aspergillus) does not worry me	0 (0.0)
2. Aspergillus resistance to azoles in hemato-oncology patients is fundamentally…	
Of clinical origin, due to the routine use of prophylaxis	41 (74.5)
Of environmental origin, due to the use of triazole compounds in agriculture	29 (52.7)
There do not seem to be resistant Aspergillus infections in hemato-oncological patients	3 (5.5)
I would not know how to say it, I lack information	3 (5.5)
*3. When do you consider it most likely that you will find yourself facing a case of secondary resistance to a broad-spectrum antifungal?**	
Patient who after a period of improvement presents clinical worsening attributed to his fungal infection	17 (31.5)
Patient who does not respond to early antifungal treatment administered for 10 days	16 (29.6)
Patient on antifungal prophylaxis who debuts with symptoms that do not respond to broad-spectrum antibiotics	15 (27.8)
The probability of secondary resistances is very low	6 (11.1)
4. In the event of suspected resistance in a patient receiving treatment for aspergillosis, what strategy would you carry out?	
Change of antifungal family to another broad-spectrum	28 (50.9)
Combined treatment with two new antifungals from different families	17 (30.9)
Association of another broad-spectrum antifungal	10 (18.2)
Increase the dose of the antifungal in use, if possible	0 (0.0)
5. The IDSA and ESCMID Guidelines recommend modifying the therapeutic strategy when the percentage of resistance of A. fumigatus against an azole is ≥10%. In your opinion, this may imply…	
A change in the choice of early treatment	48 (87.3)
A change in the choice of prophylactic treatment	17 (30.9)
In my area there are no *A. fumigatus* that show resistance to azoles	11 (20.0)
Without a previous in vitro susceptibility study, I would not worry.	2 (3.6)
6. In the face of sustained febrile neutropenia (5 days), what would you do regarding antifungal treatment?	
I would initiate it in the presence of IFI-specific pulmonary infiltrate	41 (74.5)
I would initiate it if positivity of any biomarker (GM, BDG...) regardless of the result of the imaging test (computed tomography)	37 (67.3)
I would initiate it in the presence of nonspecific or specific IFI infiltrate	23 (41.8)
I would initiate it in the absence of a pulmonary infiltrate	21 (38.2)

Answer, n (%)	Sample (N=55)
7. Regarding breakthrough IFIs in Spain…	
An increase in the incidence of mucorales has been observed	36 (65.5)
Proven ones are often resistant to previously administered antifungals	36 (65.5)
They are associated with a change in epidemiology	34 (61.8)
Mortality from IFIs has decreased	9 (16.4)
*8. Regarding the monitoring of serum levels of azoles (e.g., voriconazole), what is the situation in your hospital?**	
We obtain the results between 1 and 3 days from the taking of the sample	25 (46.3)
We obtain the results in less than 24 hours from taking the sample	12 (22.2)
We obtain the results between 4-5 days from the taking of the sample	9 (16.7)
Normally we need more than 5 days, or we do not have them	8 (14.8)
9. Some antifungals do not reach levels during the first days of their administration. In this situation, in case of IA suspicion, what strategy do you think would be the most appropriate?	
Associate an antifungal from another family and perform levels before returning to monotherapy	30 (54.5)
Check that the patient is not at risk of low levels due to interactions (e.g., dexamethasone) and maintain monotherapy	12 (21.8)
None of the options	9 (16.4)
Associate an antifungal from another family and wait for the patient's clinical improvement	4 (7.3)
10. Some of the newer targeted therapy drugs have interactions with antifungals. In this context, if indicated, what type of prophylaxis would you administer in a patient receiving midostaurin or venotoclax?	
Extended spectrum azoles	22 (40.0)
Echinocandin	21 (38.2)
Others	12 (21.8)
Fluconazole	0 (0.0)
11. If echinocandins were used as prophylaxis in a patient receiving midostaurin or venetoclax, in case of suspected gap fungal infection, what treatment would you administer?	
Liposomal amphotericin B	37 (67.3)
Isavuconazole	9 (16.4)
Voriconazole	6 (10.9)
A combined treatment	3 (5.5)
12. Regarding cryptococcosis in the hematological patient…	
I take it into account, but I have not seen recent cases in the hospital	44 (80.0)
I usually take it into account and if necessary, I carry out the necessary tests	13 (23.6)
It is underdiagnosed, it is not usually taken into account	9 (16.4)
It is not relevant in the hematological patient	3 (5.5)

BDG: 1,3-β-d-glucan; GM: galactomannan; IA: invasive aspergilosis; IFI: Invasive Fungal Infections
*1 missing value

CONCLUSION(S)

- **The present study shows that a high percentage of clinicians implicated in the management of onco-hematological patients at high risk of IFI follows the recommendations of the national and international guidelines. Most of the experts agree on:**

a) **If resistance of Aspergillus to azoles is suspected, switching to another broad-spectrum antifungal family would be the best option.**

b) **Early treatment is the best option in case of persistent febrile neutropenia (even in the presence of nonspecific or absence of lung infiltrate in CT-SCAN).**

c) **For antifungals failing to reach levels during the first days and suspected invasive aspergillosis, the most appropriate strategy would be to associate it to an antifungal from another family.**

d) **Broad-spectrum azoles and echinocandin would be a choice as prophylaxis in patients receiving new targeted therapies. Liposomal amphotericin B was the preferred option after prophylaxis with echinocandins.**

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