Pulmonary aspergillosis in hematologic malignancies: *lights and shadows*

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Fungal infections represent a very important complication observed in patients with hematologic malignancies. In a recent epidemiological multicenter survey conducted in Italy between 1999 and 2003 we observed that aspergillosis is the most frequent fungal complication among patients treated with conventional chemotherapies, followed by candidemia.[1] The same trend emerged in patients receiving allogeneic transplant, among whom aspergillosis reaches 81% of all fungal infections.[2] For this reason it must be considered *the* fungal complication in hematologic patients. Some institutions reported a predominance of *emerging aspergillus* species, such as *A. terreus* or *A. flavus*[3] but this trend was not confirmed in our experience.[1]

Clinical manifestations

The lung continues to represent the most frequently involved site. Pulmonary infection can be understood as a phenotypical representation of interaction between lowered defence mechanisms in the host and the virulence of invading fungus. Sinuses or lower respiratory tract are common portals of entry. From here a*spergillus* can first reach lung tissue and eventually spread to all other organs. Its pathogenetic mechanisms are well-known: after a colonization of the lower respiratory tract by conidia, the spores germinate and invade surrounding tissues, producing acute, necrotizing pneumonia. Frequently vascular walls are then infiltrated and the formation of fungal embolus is possible. Possible late consequences are pulmonary infarction followed by cavitation and bleeding which can be fatal.

Cough and fever are the most typical symptoms, even if patients can remain completely asymptomatic, despite the aspergillosis.[4] It is worth noting that some clinical manifestations, (i.e. hemoptysis or pneumothorax) can onset after recovering from infection. These complications are responsible for an increased risk of death even in patients with hematologic complete remission.[5-6] These two dramatic events refer to the quick increase of normal white blood cells, which induces the release of cytokines and the subsequent destruction of the vessels near the *aspergillus* ball. In these cases, angiography with vessel embolization has both a diagnostic and therapeutic role.[7]

Diagnostic procedures

The most important factor in the management of aspergillosis is a timely and correct diagnosis. It is mandatory to identify the fungal agent because of the different sensibility spectrum to available drugs. For example, voriconazole, the first-choice drug for aspergillosis, does not cover zygomycetes.

Available instruments for a correct diagnosis are microbiology, radiology and histopathology. Microbiology includes direct microscopy and culture, which are good tools but in some cases disadvantages exceed the advantages (Table 1). Some authors suggest that it could be better to perform such microbiological tests on bronchoalveolar lavage rather than on *sputum*. However, data from literature do not support this view.[8] Over recent years, other diagnostic platforms that are not based on culture have been investigated. The galactomannan antigenemia enzyme immunoassay (GM-EIA) has entered current use with discrepant results.[9-14] This variability is probably due to possible bias that could influence this test (i.e. diet, antibiotic and antifungal treatment, infection by other fungi containing a cross-reactive GM, etc.). A recent meta-analysis reported a sensitivity of 79% and a specificity of 86%, with an overall accuracy of 89%.[15] The test should be performed twice weekly and positivity is defined by at least two consecutive tests with GM index ≥0.5. Given that a negative result does not exclude the diagnosis and *viceversa*, the most correct way to use such a test is to consider GM-EIA results in the context of clinical, radiological, and laboratory findings. GM-EIA can also help improve sensitivity of microbiological tests on BAL. In a study published by Becker *et al.*,[16] in patients with IA a positivity of 100% was reported, compared to 47% achieved in serum samples. An interesting use of GM concerns a serial assessment of the test to monitor therapy.[17,18] Survival correlates with antigenemia declining during antifungal treatment; this observation can help clinicians to differentiate between patients with persistent antigenemia requiring treatment modification, and patients with progressively lower GM index who do not necessarily require any change, even when radiological images have worsened after neutrophil recovery.[19] However, prospective studies on this topic are needed. Identification of fungal species by PCR offers a wide range of identification; the use of PCR in BAL samples has been investigated with reasonable sensitivity and specificity in patients at high risk for IA (79% and 94% respectively),[20] even with higher costs compared to GM-EIA. However, many other questions should be answered before confirming the utility of PCR in the diagnosis of IA (optimal specimen type, DNA extraction method, primer specificity, PCR format): the lack of this information means these results are still difficult to interpret.[13,14, 21,22]

As for radiological tools, standard X-ray is the first line approach, even if it is not diagnostic in the majority of cases: hematologic patients typically have a decreased inflammatory response and clinical features, although variable and usually non-specific, may not manifest before the infection is far advanced. Thorax CT-scan, and particularly high resolution CT-scan (HRCT-scan), offer a better approach: different studies showed a sensitivity and specificity of nearly

Table 1. ***Lights and shadows*** **in microbiological diagnostic tools.**

Test	*Advantages*	*Disadvantages*
Microscopy	· quick · easy	· needs experience · low sensitivity · need for treatment of the sample
Culture	· useful to discriminate *aspergillus* from other filamentous *fungi* (i.e. *fusarium, scedosporium*)	· long laboratory process time · positivity at a late stage of disease · low sensitivity and specificity
GM-EIA	· good sensitivity · early indicator of infection · repeated monitoring increases sensitivity and specificity · serial assessment for monitoring of therapy	· cut-off value is under discussion · false positivity · false negativity
PCR	· identification to *species* level · high sensitivity · wide range of identification (pan-fungal)	· lack of standardization of the test (variable performance) · cost
Histology	· *gold standard* to prove aspergillosis · culture of tissue required	· frequently impracticable because of thrombocytopenia or unstable clinical conditions

GM-EIA: galactomannan antigenemia enzyme immunoassay; PCR: polymerase chain reaction.

100%.[23] HRCT-scan can give us more information about type, number, localization of lesions, and their morphological characteristics. It can demonstrate the presence of the *halo sign*, a typical precocious lesion, or the presence of the *air crescent sign*, which usually becomes more prevalent later in the course of the disease. Calliot and colleagues provide a cornerstone study. They monitored pulmonary aspergillosis with seriated lung CT-scan and described the different radiological manifestations on the basis of the time elapsed.[19] Of particular interest is a recent study showing that the presence of a *halo sign* at baseline is associated with a significantly higher global response rate and better survival.[24] This observation could have been a result of the earlier initiation of antifungal therapy in the course of the fungal disease, since the *halo sign* is the earliest radiological manifestation of invasive pulmonary aspergillosis in neutropenic patients. Despite their importance, characteristic radiological patterns do not allow us to diagnose a certain aspergillosis, because of the similarity with other angioinvasive fungi, such as *zygomycetes*, *fusarium* spp or *scedosporium* spp. Surprisingly, even non-fungal agents, such as *pseudomonas aeruginosa* and *nocardia*, can mimic aspergillosis CT-scan appearance. This makes biopsy necessary to clarify the diagnosis. A prospective study conducted by Lass-Florl and colleagues in 2003-2006, evaluated the utility of CT-guided lung biopsy for diagnosis of IFI, by combining Calcolfuor white staining, GM-EIA and PCR on biopsy specimens. This combination resulted in a fast and reliable identification of the fungus, with a specificity and sensitivity of 100%. However the utility of such a diagnostic platform is doubtful, because of the many contraindications when performing invasive procedure in hematologic patients (i.e. thrombocytopenia, hemodynamic instability).[25,26] More recently, the usefulness of PET-scan has been evaluated, but present data are very scarse.[27]

An ideal diagnostic work-up may combine both microbiological and radiological exams. Maertens *et al.* suggested an approach with a daily GM monitoring closely linked to clinical evaluation, serial sinopulmonary CT-scan and bronchoalveolar-lavage.[28] This combined work-up allowed a reduction in incorrect diagnosis of pulmonary aspergillosis. However, a similar approach is not always practicable in current practice because it is too expensive and time-consuming, and also because of a lack of general accessibility in many centers.

Treatments and guidelines

It is noteworthy that the aspergillosis mortality rate varies according to the different sites of infection. Almost all patients present with disseminated aspergillosis. An improved outcome using voriconazole treatment for central nervous system aspergillosis has been reported by Schwartz *et al.*[29] Mortality rate is instead lower for pulmonary localization.[30] During the last years we observed a stationary/increasing incidence of aspergillosis both in acute leukemia and in allogeneic transplant recipients; conversely, the mortality rate significantly decreased.[1,2] This is probably due to multiple cofactors, such as advances in diagnostic approach and new treatment options.

Different antifungal treatment approaches can be applied: prophylaxis, empirical therapy, pre-emptive therapy and target-therapy.

Recent studies evaluated the efficacy of caspofungin, voriconazole, liposomal amphotericin B, micafungin and posaconazole as prophylaxis.[31-37] However, it is still to be decided which is the best choice of treatment. Posaconazole seems to be better when compared to others, since not only is it active *in vitro*

against a wide range of yeasts (including *candida* species) and molds (including *aspergillus* species, *zygomycetes*, and *fusarium* species) but also appears to have an acceptable adverse-event profile and it is well tolerated. However, the high number of patients eligible for prophylaxis and the long mean duration of such a treatment makes it a very expensive strategy, limiting its use. It would be necessary to define the population for whom prophylaxis would be most beneficial also on the basis of local epidemiology.[38]

An empirical approach implies the commencement of antifungal therapy at the first clinical suspicion of a possible fungal infection (generally a persistent fever despite broad-spectrum antibiotics). Some authors believe this approach results in significant overtreatment and expenditure, and in an increasing incidence of breakthrough fungal infections. Maertens *et al.*[22] indicated the pre-emptive approach supported by a more intensive use of surrogate markers of aspergillosis (i.e. abnormalities in CT-scan findings, antigen assay) as an ideal strategy in an attempt to reduce exposure to antifungal agents. However, a recent randomized study by Cordonnier *et al*. showed that the empirical approach could have the same efficacy at the same cost.[39]

Reviewing data from literature, first and second line antifungal approaches were suggested in treating pulmonary aspergillosis. The US Food and Drugs Administration (FDA) and the European Medicines Agency (EMEA) approved only for aspergillosis voriconazole and L-AMB for first line treatment, leaving caspofungin and posaconazole for the salvage therapy. Over the last few years, however, several studies have been conducted where these latter and other antifungal drugs have been used in first line therapy.[40-47] Efficacy data of some of these studies are summarized in Table 2. In our opinion, reported percentages of responders could be different from those really observed in clinical practice because of a selection bias in the enrollement of patients in experimental trials and the very restrictive criteria for the evaluation of response.

Following published randomized studies, guidelines by several co-operative groups and international societies (i.e IDSA, ECIL etc) have been revised, to summarize the current evidence for treatment of aspergillosis (Table 3).[48,49] Table 3 reports a comparison of the strength of recommendation and quality of evidence of the different groups for the use of antifungal agents in primary and salvage therapy of invasive pulmonary aspergillosis. All the guidelines are concordant in recommending voriconazole as the drug of choice for the primary treatment of invasive pulmonary aspergillosis (AI). L-AMB is also considered an alternative primary therapy in some patients in all guidelines, even though with a different grade of recommendation. L-AMB, ABLC, caspofungin, posaconazole and itraconazole are indicated in salvage therapy for patients refractory to or intolerant of primary antifungal therapy. Combination therapy of invasive fungal infections is attractive from the perspective of synergistic potential, but in the absence of a well-controlled, prospective clinical trial, its use for primary therapy is not routinely recommended. It is, however, recognized to have a possible role, with different recommendation grades, in salvage therapy.

Surgery should also be considered as a possible treatment option for pulmonary aspergillosis. In the different guidelines, surgical resection of aspergillus-infected tissue is indicated as useful in patients with lesions that are contiguous with the great vessels or causing hemoptysis. It is then suggested in patients with a documented aspergillosis (i.e. a single nodule) who have a transplant program, due to their propensity to reactivate in the setting of continued immuno-

Table 2. Efficacy of different antifungal drugs in invasive aspergillosis (data about pulmonary localization only).

Ref.	*Antifungal agent*	*N. cases of aspergillosis*	*OR (%)*	*N. cases of pulmonary aspergillosis*	*OR (%)*
		Front-line therapy			
Herbrecht *et al.*[40]	d-AmB	133	32%	117	34 %
	Voriconazole	144	53%	123	55 %
Candoni *et al.*[41]	Caspofungin	32	56%	32	56 %
Viscoli *et al.*[42]	Caspofungin	61	33%	60	32 %
Cornely *et al.*[43]					
L-AmB SD	107	50%	98	51 %	
	L-AmB HL	94	46%	84	48%
		Salvage therapy			
Maertens *et al.*[44]					
Caspofungin	83	45%	64	50 %	
Walsh *et al.*[45]	Posaconazole	107	42%	79	39 %
Maertens *et al.*[46]					
Combined*	53	55%	43	58 %	

*d-AmB: deoxycolate-amphotericin B; L-AmB: liposomal-amphotericin B; SD standard –dosing, HL high loading - dosing; OR: overall response (complete response + partial response). *Caspofungin plus AmB formulation or plus azoles.*

Table 3. Comparison among the strength of recommendation and quality of evidence of IDSA and ECIL for antifungal agents in primary and salvage therapy of invasive pulmonary aspergillosis is reported.

	IDSA 2008[49]	*ECIL 2007* [§50]
Voriconazole	AI	AI
L-AmB	AI	BI
ABLC	–	BI
Caspofungin	–	CIII
Itraconazole	–	CIII
d-AmB	–	DI
Posaconazole	–	–
Combination therapy	BII	DIII
Surgery	BIII	CIII
Salvage therapy		
Caspofungin	BII	BII
Voriconazole	^	BII[@]
Posaconazole	BII	BII
L-AmB	AII	BIII
ABLC	AII	BIII
Itraconazole	BII	CIII
Combination therapy*	BII	CII

*[§]Update ECIL-2 2007; [@]if not used in 1st line; *Caspofungin+ L-AmB or Caspofungin + Voriconazole; no data about AmB (any formulation) + azole; -- not reported for primary therapy; ^ not indicated if used as primary treatment.*

Strength of recommendation
A Good evidence to support a recommendation for use.
B Moderate evidence to support a recommendation for use.
C Poor evidence to support a recommendation for use.
D Moderate evidence to support a recommendation against use.
E Good evidence to support a recommendation against use.

Quality of evidence
I Evidence from at least one properly randomized, controlled trial.
II Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time series; or from dramatic results of uncontrolled experiments.
III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

N.B: IDSA 2008 guidelines censored strength of recommendation D and E.

suppression.[50]

The new IDSA takes granulocyte transfusions into consideration for the treatment of patients with invasive pulmonary aspergillosis.[51,52] The rationale for improved outcome appears to be an adequate number of granulocytes transfused to the profoundly neutropenic patient. The real benefit of this procedure is not clarified and a precise grade of recommendation is lacking in IDSA guidelines. This option is, however, considered to be useful in the course of very severe refractory infections. In our opinion, one of the problems of this procedure in patients with acute leukemia is the possible immunization if relatives are used as donors since this could preclude a future allogeneic stem cell transplantation.

Final consideration

In conclusion, the population of patients at risk for pulmonary aspergillosis is expanding; it continues to represent the most relevant fungal complication. The emergence of other molds and yeasts observed in some centers has not been confirmed worldwide. The introduction of new antifungal molecules has modified patients' life-expectancy. However, outcome should be further improved by establishing a more timely diagnosis and anticipating targeted therapy. Many questions remain unanswered about the optimal treatment of such a complication, in particular about the management of refractory patients and the utility of combined therapies.

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