

Diagnosing invasive pulmonary aspergillosis in COPD patients: more challenging and less rare than before. A review of the literature

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ABSTRACT:

— Invasive pulmonary aspergillosis (IPA) is a life-threatening infection first described among neutropenic hematological patients. It is the most frequent form of invasive fungal infection caused by the filamentous fungi species named *Aspergillus*.

Classically, patients at risk are those with prolonged neutropenia, recipients of hematopoietic stem-cell transplants or solid-organ transplants, and patients with immunodeficiency (e.g. AIDS, chronic granulomatous disease). During the last decade, it became increasingly clear that IPA is not only an opportunistic infection of the neutropenic patients but that it could affect other groups of patients having different clinical and anatomical/pathological manifestations.

Patients with chronic obstructive pulmonary disease (COPD) represent a very challenging group of patients because of the frequency and the difficulty in diagnosing this illness.

We propose a review of the recent literature concerning the diagnosis of IPA among patients with COPD.

— **Keywords:** Chronic obstructive pulmonary disease, COPD, Invasive pulmonary aspergillosis, IPA, Diagnosis, Review.

INTRODUCTION

Invasive pulmonary aspergillosis (IPA) is a life-threatening infection first described among neutropenic hematological patients. It is the most frequent form of invasive fungal infection caused by the filamentous fungi species named *Aspergillus*.

Classically, patients at risk are those with prolonged neutropenia, recipients of hematopoietic stem-cell transplants or solid-organ transplants, and patients with immunodeficiency (e.g. AIDS, chronic granulomatous disease). During the last decade, it has become increasingly clear that IPA is not only an opportunistic infection affecting neutropenic patients but it could affect other groups of patients and present with different clinical and anatomopathological manifestations.

Advanced COPD is correlated with a higher risk of IPA. Patients in stages III and IV, according to the Global Initiative for Chronic Obstructive Lung Disease

(GOLD) criteria for severity of COPD, are at risk of IPA¹⁻⁴, especially when admitted in intensive care unit (ICU).

In the EORTC/MSG definitions of invasive fungal diseases, predisposing host factors were extended to include prolonged use of corticosteroids⁵. A cumulative corticosteroid dose as high as 700 mg of prednisone or the equivalent prior to the time of admission, which is very frequent among COPD patients with a GOLD stage \geq III, seems to be associated with a higher risk of IPA^{1,6}.

Furthermore, due to bacterial exacerbations, COPD patients frequently receive broad-spectrum antibiotics. The use of antibiotics within 3 months before admission for IPA was found to be a significant predictor of IPA in patients with COPD¹. In this particular setting, the correlation between IPA and COPD has been clearly demonstrated. Several studies in the last 15 years have shown that up to 55% of patients admitted to ICU for an exacerbation of COPD had finally an IPA⁷. In an univer-

sity hospital, the authors conducted autopsies on 222 patients that failed in ICU during one year, and among the 6 patients failing for IPA 5 had COPD⁸. In a prospective Chinese study, IPA was the final cause of the 2% of all the admissions for COPD exacerbation during 2 years in a tertiary hospital⁶.

IPA is often underestimated among COPD patients and there is a delay in diagnosis. The reported mortality rate of IPA in COPD patients ranges from 72% to 95%^{1,3,9}. In a Turkish tertiary hospital, IPA was the diagnosis of 15.4% of the admissions for COPD and it was usually diagnosed 13.8 days after admission¹⁰. Evaluating survival rate at 120 days in a Spanish tertiary hospital it was 28% among the admitted for COPD having an IPA (median 29 days; 95% CI 20.59-37.40), and 75% (median 86 days; 95% CI 61.13-110.86) among admitted for COPD without IPA¹.

Patients with chronic obstructive pulmonary disease (COPD) represent a very challenging group because of the frequency and the difficulty of diagnosis. Unlike neutropenic patients in whom IPA mainly has an angio-invasive pattern, the dominating pattern in non-neutropenic patients (as COPD patients) is airway-invasive¹¹. This leads to a difficult interpretation of radiological findings that appear less specific and lack the classical IPA signs. Also, the classical microbiological tests used for making a diagnosis, such as cultures of sputum or bronchial wash and galactomannan in serum and bronco-alveolar lavage fluid, show less sensibility and specificity, probably due to higher *Aspergillus* colonization rate of the airway and a better clearance by circulating neutrophils along with less angio-invasiveness¹².

In this paper, we review the literature on the diagnosis of IPA among COPD patients.

CLINICAL PRESENTATION

No pathognomonic clinical presentation of IPA exists in COPD patients. The most frequent clinical sign is a nonspecific antibiotic-resistant pneumonia with exacerbated dyspnea.

COPD patients at risk of having an IPA are those chronically treated with corticosteroids and an advanced disease (GOLD stage \geq III)¹⁻⁴. The main symptoms collected across the most important clinical series of COPD patients with IPA are summarized in Table 1. Typically, COPD patients are less likely to have fever (10% to 46%)^{1,13-15} than neutropenic patients (up to 87%)¹⁶ at the presentation of IPA. Probably, fever is partially masked

by corticosteroids that almost all the COPD patients were taking during admission. The most frequently reported symptom is a worsening dyspnea during COPD exacerbation. It is the main symptom in all the studies with a prevalence of up to 90%^{1,13,14}. Wheezing with an increase of sputum production is a frequent sign but it is also typical of many other causes of COPD exacerbation. One patient out of 10 complains of chest pain and episodes of hemoptysis.

LABORATORY FINDINGS

Few analytical reports are available in the literature. There are no analytical findings specific for IPA. The increase of inflammatory markers (white blood cells, CRP, LDH, and fibrinogen) is typical. In precedent reviews of case series, leukocytosis (WBC $>$ 12000/ml) was present in 53%³ and 77%¹ of patients and a mean WBC count of 21000¹⁵, 17400⁴ and 11000¹³ was reported.

RADIOLOGICAL FINDINGS

The golden standard for radiologic diagnosis of IPA is chest Computed Tomography (CT).

Chest radiograph could be a useful diagnostic tool. On admission, it was reported as abnormal in 78% of patients by Samarakoon et al⁴; but it could have low sensitivity in the earlier stage of IPA. In a Japanese study, for example, thoracic CT scan abnormalities preceded chest radiograph by 4.7 days¹⁷.

Both exams have a lower specificity in non-hematological patients for the rarity of pathognomonic signs, well established in hematological patients⁵. The sensitivity of the air crescent sign and the halo sign has been reported as very low for non-neutropenic patients (from 5% to 24%)¹⁸⁻²⁰. Moreover, confounding factors from the underlying COPD can make more difficult to recognize specific images. In a case-control study, where all the patients had COPD with the case-group having IPA and the control-group not, Xu et al¹³ showed that there were no statistically significant differences in radiologic abnormalities between the two groups, neither in chest radiograph (infiltrates, nodules, cavitations, consolidations) nor in CT scan (halo sign, infiltrates, nodules, cavitations, consolidations). This is true during COPD exacerbation, but when Barberan et al² compared COPD patients with IPA and COPD patients just colonized they found significant differences. In the IPA-COPD group,

Table 1. Main symptoms of IPA in COPD patients.

	Dyspnea	Wheezing	Fever	Hemoptysis	Chest pain
Bulpa et al (2007) ³	100%	78.6%	38.5%	41.7%	–
Guinea et al (2010) ¹	94.3%	–	33.9%	9.4%	16.9%
Delsuc et al (2015) ¹⁴	98%	–	12%	10%	–
Xu et al (2012) ¹³	93.3%	80%	10%	–	–
He et al (2011) ¹⁵	–	85%	46%	15.4%	15.4%
Samarakoon et al (2008) ⁴	32%	8%	–	15%	8%

there was a significantly higher percentage of patients (vs. colonized) presenting infiltrates (72.9% vs. 42.9%, $p < 0.001$) and cavitations (12.5% vs. 0%, $p < 0.004$) in X-ray. Infiltrates, nodules and a “tree-in-bud” pattern are the most frequent radiological findings across the studies. In particular infiltrates are present in 34% to 77% of the cases^{1,2,4,13,15}. The most relevant radiological findings are shown in Table 2.

In all these series, worsening radiological patterns was more prevalent in patients with IPA, suggesting that both chest radiograph and CT scan should be repeated during the admission in the suspect of IPA, looking for rapid radiological changes.

MICROBIOLOGY

Direct microbiological diagnosis

Direct examination and cultures of different specimens (sputum, BAL, blood, biopsy) are still important tools for diagnosing IPA.

Direct examination of sputum specimens, stained with calcofluor white, should always be performed even if the presence of *Aspergillus spp* in sputum of COPD patients does not have the same diagnostic value as in neutropenic patients. In a study, the positive predictive value (PPV) of lower respiratory tract cultures was higher in granulocytopenic patients (72%) compared with solid organ transplant recipients and patients receiving glucocorticoids (58%)²¹.

Due to high colonization rate and the airway-invasive pattern in COPD patients, the performance of culture of sputum or bronchial wash is poor. A possible option to improve the diagnosis of IPA is the culture of bronchoalveolar lavage fluid (BALF), as evidenced by Fortun et al²². They enhanced specificity and PPV of cultures from 65.4% and 35.7% (sputum/bronchial wash) to 96.2% and 88.9% (BALF culture), respectively²².

The most common isolates are *A. fumigatus* (84%), *A. niger* (8%) and *A. flavus* (8%)⁴.

Positive cultures from normally sterile sites and direct examination of biopsy demonstrating invasion of tissue by hyphal elements are still the only way to diagnose a proven IPA with certainty.

Unfortunately, biopsies often cannot be obtained due to the severity of clinical status and the risk of bleeding.

Blood cultures should always be performed but have a very low sensitivity. They are positive in less than 10% of proven cases⁴.

Indirect microbiological diagnosis

GM

Galactomannan (GM) is a polysaccharide that is a major constituent of *Aspergillus* cell walls.

The Platelia[®] galactomannan assay is the approved test using the serum and bronchoalveolar lavage fluid (BALF). It consists in a double-sandwich enzyme immunoassay (EIA) with an antibody that detects multiple epitopes on galactofuranose side chains of galactomannan. Although it is considered the most “*Aspergillus*-specific” assay, GM positivity can occur with multiple conditions, including infection with other fungi.

It is important to remember that performance of GM is affected by mould-active antifungal agents²³ and by inconsistencies in the diagnostic yield of BAL²⁴. To obtain more reliable results, BAL should be performed using standardized protocols²⁵ and before the beginning of an empirical therapy.

Serum GM

The lower sensitivity of serum GM in non-hematological patients is well known. According to a recent systematic review²⁶, the sensitivity of serum GM in this setting of patients was < 50%.

Several studies confirmed this trend also in COPD patients showing a sensitivity ranging between 30% and 60%^{1,15,27}.

Among all the possible explanations, the two most important factors should be an increased clearance by circulating neutrophils and a lower angio-invasiveness of IPA among COPD patients¹².

BALF GM

Nowadays, bronchoalveolar lavage (BAL) appears an essential exam for the diagnosis of IPA in COPD patients.

As underlined above, GM has a poor diagnostic value if measured only in serum samples but it could be very useful in BALF, even if evidence is limited in COPD patients and the threshold values are not clearly established^{7,18,22,28}.

In fact, almost all the evidence has been collected in hematological patients among whom a cut-off of GM-BALF ≥ 1.0 seems to be the optimal one^{29,30}.

Table 2. Radiological findings of IPA in COPD patients.

	Chest X-ray					CT scan				
	Xu ¹³	Bulpa ³	Guinea ¹	Barberan ²	He ¹⁵	Xu ¹³	Bulpa ³	Guinea ¹	Barberan ²	He ¹⁵
Infiltrates	34.6%	–	54.7%	72.9%	76.9%	70.6%	–	18.8%	77.8%	50%
Nodules	11.5%	6%	20.7%	25%	38.4%	23.5%	12.5%	18.8%	58.3%	100%
Cavitation	3.8%	6%	16.9%	12.5%	7.6%	17.6%	12.5%	–	30.6%	16.6%
Consolidation	7.7%	75%	22.6%	–	53.8%	17.6%	–	–	–	66.6%
Halo sign	–	–	–	–	–	5.9%	6%	5.7%	5.6%	16.6%

For non-hematological patients, D'Haese et al³¹ proposed an optimal cut-off of 0.8 in their cohort of 251 mixed patients, 79.3% no hematological, but none of them had COPD.

In a study of COPD patients in ICU, He et al²⁸ found an optimal ODI for BALF GM of 0.8, with sensitivity, specificity, and positive and negative predictive values of 88.9%, 100%, and 100% and 94.4%, respectively²⁸.

In a recent multicenter study, Fortun et al²² showed that in the subgroup of COPD patients a cut-off of 0.5 (sensitivity, 88.9%; specificity, 88.4%; PPV, 72.7%; and NPV, 95.8%) performed better than BALF GM ODI \geq 1.0²².

Beta-D-glucan assay

1,3-Beta-D-glucan (BDG) is a cell-wall component of many fungi, and it is detected by the beta-D-glucan assay. This test utilizes a reaction between free circulating BDG and a zymogen that induces a coagulation cascade and has been used to detect BDG in the serum and plasma. It has good accuracy for distinguishing patients with proven or probable invasive fungal infections from patients without invasive fungal infection³².

This test is very useful for invasive candidiasis, probably less useful for other invasive fungal infections (IFI). There are no sufficient data to establish an optimum cut-off for IPA in non-neutropenic patients because studies and meta-analysis were conducted mostly on patients with invasive candidiasis and just a little number of invasive aspergillosis.

A study compared the performance of the GM EIA with the BDG assay in sera from 105 patients with invasive aspergillosis, demonstrating a higher specificity with the GM test (97% versus 82%) but a lower sensitivity (81% versus 49%)³³. Nevertheless, all the patients were hematological neutropenic patients.

A Chinese study³⁴ with 27 proven/probable IPA in non-neutropenic patients combined BDG and GM. When used alone, sensitivity and specificity were 48% and 78% for BGD and 40% and 89% for GM, respectively. If used together, considering a true IPA only when both exams were positive, sensitivity and specificity were 18% and 92%, respectively. On the other hand, if just one of the two was considered for diagnosing IPA sensitivity and specificity yielded 70% and 75%, respectively³⁴.

PCR and LFD

Aspergillus polymerase chain reaction (PCR) and lateral flow device (LFD) are two promising investigational assays.

Different technologies and microbial targets have been reported for PCR. In a meta-analysis of 25 studies, sensitivity and specificity of PCR in serum were 84% and 76%, respectively³⁵.

PCR could be a useful diagnostic tool when investigators would agree on methodology and interpretation.

LFD uses a mouse monoclonal antibody, known as JF5, to detect a mannoprotein found in the serum and BAL. Early clinical trials and meta-analysis suggest that LFD should be an alternative to BAL GM, with the additional advantages that it is easy to use, requires no technical expertise for its performance and has a very quick turn-around of results.

Ongoing studies will report on the reliability of LFD (e.g. NCT02058316).

DISCUSSION

COPD is a frequent disease, which has been projected that it will become the third leading cause of death worldwide by 2020³⁶.

The main cause of admission for COPD is exacerbation, mostly due to infections of the lower respiratory tract (LRT). IPA is one of the possible causes of COPD exacerbation, less rare than thought and probably the worst one.

Patients at risk of having IPA are those with advanced disease (GOLD stage \geq III)¹⁻⁴. Both high rates of *Aspergillus* colonization of the LRT and chronic use of corticosteroids represent the principal background for the risk of IPA. It is estimated that 22.1% of COPD patients with a positive LRT culture for *Aspergillus* will have an IPA¹. Furthermore, COPD patients frequently receive treatment with broad-spectrum antibiotics for COPD exacerbations and sometimes the exacerbation led to an admission in ICU.

Diagnosing IPA in COPD patients is very difficult for several reasons. IPA is often underdiagnosed because not suspected in COPD patients.

It is proven that all the radiological and microbiological findings that are well established for neutropenic patients have a lower sensitivity in COPD patients.

Isolation of *Aspergillus* spp does not have the same meaning than in neutropenic patients, due to the higher rate of the LTR colonization in COPD patients.

Also, indirect microbiological methods are less sensitive. The sensibility of serum GM in this setting is very low and there is no universal agreement for an optimal clinical cut-off for BALF-GM. Many meta-analyses demonstrated that the optimal cut-off for BALF-GM is \geq 1 in neutropenic patients. This is not clear in non-neutropenic patients (especially in COPD setting). Many authors have proposed different cut-offs (e.g. 0.8²⁸, 0.5²²) but more data are needed to validate them. Other newer tests such as PCR and LFD, even if promising, seem to be less sensitive and specific in non-neutropenic patients.

The radiological golden standard for IPA diagnosis is CT chest scan. Classical IPA signs ("halo sign", "air crescent sign") are currently observed in less than 6%^{1-3,13} of IPAs in COPD patients. The most frequent radiological findings are unspecific infiltrates and consolidations^{1,2,4,13,15} that could be confounded for other causes of pneumonia in COPD exacerbations.

CONCLUSIONS

To sum up, IPA must be suspected in all COPD patients admitted for an exacerbation, especially in ICU and if they have an advanced disease (GOLD stage \geq III). In the suspicion of IPA, a CT scan should be performed looking for specific (“halo sign”, “air crescent sign”) and non-specific (infiltrates, nodules, “tree-in-bud”) signs. CT scan should be repeated during hospitalization because worsening radiological findings are typical of IPA. Both direct and indirect microbiological tests are crucial. Cultures of BALF should support classical sputum and blood cultures and the direct observation of LRT specimens. GM appears, at this moment, as the best indirect microbiological test. Specimens such as serum GM, BALF-GM should always be obtained and evaluated, knowing that cut-offs lower than 1 are probably needed for COPD patients^{28,22}. If possible, a second indirect test (PCR, LFD) is useful in combination with GM to increase sensitivity and specificity³⁷.

Finally, due to the difficulty of the diagnosis, a well-trained infectious diseases specialist should always be consulted to evaluate the results.

DISCLOSURES:

The authors declare that they have no potential conflicts of interest.

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