

Invasive Pulmonary Aspergillosis in Chronic Obstructive Pulmonary Disease Exacerbations

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Abstract

Nowadays, reports in the literature support that patients with severe chronic obstructive pulmonary disease (COPD) are at higher risk to develop invasive pulmonary aspergillosis (IPA). However, the interpretation of *Aspergillus*-positive cultures from the airways in critically ill COPD is still a challenge. Indeed, as the patient could be merely colonized, tissue samples are required to ascertain IPA diagnosis but they are rarely obtained before death. Consequently, diagnosis is often only suspected on the basis of a combination of three elements: clinical characteristics, radiological images (mostly thoracic CT scan), and microbiological, and occasionally serological, results. To facilitate the analysis of these data, several algorithms have been developed, and the best effectiveness has been demonstrated by the Clinical algorithm. This is of importance as IPA prognosis in these patients remains presently very poor and using such an algorithm could promote prompter diagnosis, early initiation of treatment, and subsequently improved outcome.

While the most classical presentation of IPA in critically ill COPD patients features a combination of obstructive respiratory failure, antibiotic-resistant pneumonia, recent or chronic corticosteroid therapy, and positive *Aspergillus* cultures from the lower respiratory tract, the present article will also address less typical presentations and discuss the most appropriate treatments which could alter prognosis.

Keywords

- ▶ *Aspergillus*
- ▶ invasive pulmonary aspergillosis
- ▶ COPD
- ▶ exacerbation

Chronic obstructive pulmonary disease (COPD) patients frequently experience acute exacerbations of COPD (AECOPDs) which may require hospitalization. These AECOPDs most often link to an infectious origin, mainly viral or bacterial. However, reports have focused on *Aspergillus* infections as a possible cause for acute respiratory deterioration, essentially in COPD patients under steroid therapy.¹ Due to progressive respiratory failure, these patients often require intensive care unit (ICU) admission for ventilatory support.

Contrasting with oncohematological patients,² data remain limited in the literature, but recent epidemiologic and autopsy data have been published. As in hematological and solid-organ transplant patients,³ the mortality rate remains high (1, AspICU project, data on file⁴). Thus, early diagnosis and initiation of treatment seem key to enhance prognosis.⁵ But, as the presence of *Aspergillus* spp. in the airways does not equate to infection,¹ the diagnosis of invasive pulmonary aspergillosis (IPA) remains a challenge and consequently IPA diagnosis

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habitually relies on a cluster of clinical, laboratory, and radiological findings. Therefore, this review will discuss the epidemiology, clinical signs, laboratory findings, and diagnostic procedures to facilitate rapid recognition of IPA in COPD patients to initiate antifungals as early as possible.

IPA Definitions

Clinical diagnosis of IPA remains a challenge, as the most frequently used diagnostic criteria (defined by the European Organization for Research and Treatment of Cancer/Mycosis Study Group [EORTC/MSG]) were developed for research purposes and not for daily clinical practice. Moreover these definitions focus on the classic “at risk” population with hematological and oncological malignancies and are, as such, not appropriate for COPD or critically ill patients.⁶ To address this issue, the EORTC/MSG algorithm was recently adapted twice resulting in the elaboration of the algorithm for COPD patients (COPD algorithm)¹ and the Clinical algorithm for ICU patients.^{7,8} The latter was subsequently externally validated in a large population of ICU patients,⁴ and the three were compared in a large cohort of ICU patients with COPD. In that cohort, the Clinical algorithm demonstrated greater accuracy to detect IPA than the COPD one. In turn, both algorithms had greater diagnostic value than the EORTC/MSG criteria (► **Table 1**).⁹

Epidemiology

Despite increasing cases reported in the literature, the incidence of IPA in COPD patients remains poorly documented. This is mainly due to the lack of a consistent case definition and the absence of specific surveillance efforts. To facilitate the diagnosis, several authors have developed diagnostic criteria,^{1,4,6} but their use is not yet generalized. In addition, as the growth of *Aspergillus* spp. can be interpreted as mere colonization in COPD patients, IPA diagnosis could be delayed.¹ A large review reported that approximately 1% of patients with invasive aspergillosis (IA) suffered from COPD.¹ However, in a large study of IPA in ICU patients, COPD was the underlying condition in 34% of patients suffering from IPA.¹⁰ In a more recent autopsy study, IPA was diagnosed in 2.8% of patients while 44% suffered from COPD.¹¹ Finally, Guinea et al reported a growth of IPA cases among these patients (from 0.7% in 2000 to 1.3% in 2007).¹²

Correlation between the daily dose of corticosteroids and the probability to develop IA was investigated by several authors. Pooling the data from the literature, more than 20 mg prednisone per day or a cumulative dose of more than 700 mg was associated with an increased risk of infectious complications.¹³ However, for COPD patients, precise dosages or durations of corticotherapy as a risk factor for IPA cannot be

Table 1 Diagnostic criteria for invasive pulmonary aspergillosis according to the COPD,¹ clinical,⁸ and the European Organization for the Research and Treatment of Cancer/Mycosis Study Group⁶ algorithms

<p>COPD algorithm</p> <ul style="list-style-type: none"> • <u>Proven invasive pulmonary aspergillosis</u> Histopathological or cytopathological examination, from needle aspiration or biopsy specimen obtained from any pulmonary lesion present for <3 months, showing hyphae consistent with <i>Aspergillus</i> and evidence of associated tissue damage, if accompanied by any one of the following: <ol style="list-style-type: none"> 1. Positive culture of <i>Aspergillus</i> spp. from any LRT sample. 2. Positive serum antibody/antigen test for <i>A. fumigatus</i> (including precipitins). 3. Confirmation that the hyphae observed are those of <i>Aspergillus</i> by a direct molecular, immunological method and/or culture. • <u>Probable invasive pulmonary aspergillosis</u> As for proven IPA but without confirmation that <i>Aspergillus</i> is responsible (points 1, 2, and 3 are not present or tested). OR COPD patient, usually treated with steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea,^a suggestive chest imaging^b (radiograph or CT scan; <3 months^c), and one of the following: <ol style="list-style-type: none"> 1. Positive culture^d and/or microscopy for <i>Aspergillus</i> from LRT. 2. Positive serum antibody test for <i>A. fumigatus</i> (including precipitins). 3. Two consecutive positive serum galactomannan tests. • <u>Possible invasive pulmonary aspergillosis</u> COPD patient, usually treated by steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea,^a suggestive chest imaging^b (radiograph or CT scan; <3 months^c), but without positive <i>Aspergillus</i> culture or microscopy from LRT or serology. <ul style="list-style-type: none"> • <u>Colonization</u> COPD patient with positive <i>Aspergillus</i> culture from LRT without exacerbation of dyspnoea, bronchospasm, or new pulmonary infiltrate.
<p>Clinical algorithm</p> <ul style="list-style-type: none"> • <u>Proven invasive pulmonary aspergillosis</u> Microscopic analysis on sterile material: histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or sterile biopsy in which hyphae are seen accompanied by evidence of associated tissue damage. Culture on sterile material: recovery of <i>Aspergillus</i> by culture of a specimen obtained by lung biopsy. • <u>Putative invasive pulmonary aspergillosis (all four criteria must be met)</u> <ol style="list-style-type: none"> 1. <i>Aspergillus</i>-positive lower respiratory tract specimen culture (= entry criterion) 2. Compatible signs and symptoms (one of the following):

Table 1 (Continued)

<ul style="list-style-type: none"> – Fever refractory to at least 3 days of appropriate antibiotic therapy – Recrudescence fever after a period of defervescence of at least 48 hour while still on antibiotics and without other apparent cause – Pleuritic chest pain – Pleuritic rub – Dyspnea – Hemoptysis – Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support <p>3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs</p> <p>4. Either 4a or 4b</p> <p>4a. Host risk factors (one of the following conditions):</p> <ul style="list-style-type: none"> – Neutropenia (absolute neutrophil count < 500/mm³) preceding or at the time of ICU admission – Underlying hematological or oncological malignancy treated with cytotoxic agents – Glucocorticoid treatment (prednisone equivalent, >20 mg/d) – Congenital or acquired immunodeficiency <p>4b. Semiquantitative <i>Aspergillus</i>-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae</p> <ul style="list-style-type: none"> • <i>Aspergillus</i> respiratory tract colonization <p>When ≥1 criterion necessary for a diagnosis of putative IPA is not met, the case is classified as <i>Aspergillus</i> colonization.</p>
<p>EORTC/MSG algorithm</p> <ul style="list-style-type: none"> • <u>Proven invasive pulmonary aspergillosis</u> <p>Idem Clinical algorithm</p> <ul style="list-style-type: none"> • <u>Probable invasive pulmonary aspergillosis (all three criteria must be met)</u> <ol style="list-style-type: none"> 1. Host factors (one of the following): <ul style="list-style-type: none"> – Recent history of neutropenia (<500 neutrophils/mm³) for >10 days – Receipt of an allogeneic stem cell transplant – Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/d of prednisone equivalent for >3 wk – Treatment with other recognized T-cell immunosuppressants – Inherited severe immunodeficiency 2. Clinical features (one of the following three signs on CT): <ul style="list-style-type: none"> – Dense, well-circumscribed lesion(s) with or without a halo sign – Air-crescent sign – Cavity 3. Mycological criteria (one of the following): <ul style="list-style-type: none"> – Direct test (cytology, direct microscopy, or culture) on sputum, BAL fluid, bronchial brush indicating presence of fungal elements or culture recovery <i>Aspergillus</i> spp. – Indirect tests (detection of antigen or cell-wall constituents): galactomannan antigen detected in plasma, serum, or BAL fluid • <u>Possible invasive pulmonary aspergillosis</u> <p>Presence of host factors and clinical features (cf. probable invasive aspergillosis) but in the absence of or negative mycological findings.</p>

Abbreviations: BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; CT, computed tomography; EORTC/MSG, European Organization for the Research and Treatment of Cancer/Mycosis Study Group; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; LRT, lower respiratory tract.

^aExacerbation of dyspnoea and/or bronchospasm resistant to appropriate treatment including antibiotics.

^bPulmonary lesion(s) unresponsive to appropriate antibiotics (refers to dose, route, spectrum, and activity against cultured bacteria).

^cPulmonary lesions, especially cavitory, present for >3 months are better classified as chronic pulmonary aspergillosis, unless direct tissue invasion is demonstrated.

^dStandard or sabouraud culture, or molecular detection test when licensed.

deduced from the literature, but risk for IPA has been associated with high doses and/or prolonged administration of steroids.^{14–17} Additionally, some reports have suggested that high doses of inhaled corticosteroids may also promote IPA.^{18–20} Therefore, in severe COPD, the risk of side effects of inhaled steroids (particularly infections related to immune system perturbations) must be weighed against the expected and well-proven respiratory benefits. Furthermore, COPD patients can as well develop IPA without prior corticosteroid exposure.²¹

In addition, there is now a growing body of evidence to support that infections, in particular viral infection such as influenza^{22,23} or cytomegalovirus, may promote IPA.²⁴

Pathophysiology

Aspergillus spp. is a worldwide airborne pathogen with spores small enough (2–3 μm) to reach lung parenchyma via the airways. In COPD patients, the defense mechanisms of the airways, which normally clear out the majority of *Aspergillus* conidia, are impaired by tobacco smoke (through alteration of the ciliary activity of the bronchial epithelium), and by repeated epithelial damages due to iterative episodes of infection. These lesions enable the binding of conidia to the epithelial layer.²⁵ Thus, in contrast to hematological patients where *Aspergillus* dissemination is a bloodborne process, the bronchial mucosa is first invaded, then the contiguous lung

parenchyma, and finally the vasculature-inducing secondary pulmonary infarction.

The immune system, especially alveolar macrophages (AM) and neutrophils, fulfills a key role in the destruction of the *Aspergillus fumigatus* conidia principally by AM and of the hyphae and germinating spores by neutrophils.^{26–30}

Mechanisms and sequence of the conidia destruction by AM have been extensively investigated.^{30–33} By inhibiting AM and neutrophil antifungal activities, steroids facilitate the onset of IPA, and, by themselves, boost the growth of some *Aspergillus* spp. (especially *A. fumigatus*).^{33–36} Additionally, corticosteroids modify the TH1-TH2 cytokine response to infection and thus reduce the defenses against *Aspergillus*.³⁷

In an experimental model with corticosteroid-exposed animals, histological examinations of IPA lesions in the lung parenchyma showed large foci of pneumonia, exudative bronchiolitis with bronchial and alveolar destructions, and hemorrhagic necrosis with neutrophil infiltration,^{29,38} with only few *Aspergillus* detected and, when present, typically in their non-germinated form. Thus, the corticosteroid-treated animals, unlike neutropenic ones, appear to die from a disproportionate host reaction rather than the fungal invasion itself. These observations could enlighten, at least partially, why pneumonia is the main lesion identified in histological examinations, and therefore that in corticosteroid-treated COPD patients, chest X-rays more often demonstrate nonspecific consolidations than multiple nodules.¹

In addition, in these patients, hematogenous metastasis seems unusual as both autopsy studies in COPD patients and findings from IPA models in animals under corticosteroids, finally, rarely reported disseminated aspergillosis.^{1,29,38}

Furthermore, in the setting of sepsis and septic shock, which remains one of the most frequent causes for ICU referral, the immune response is biphasic and could explain why some COPD patients without apparent immunodepression may acquire IPA. Indeed, sepsis is divided into two phases: an initial hyperinflammatory response followed by an anti-inflammatory phase. When the latter reaction is disproportionate, it leads to the known compensatory anti-inflammatory response syndrome (CARS) characterized by immunoparalysis. As a consequence, the patient is temporarily immunocompromised and thus at increased risk for opportunistic infections such as IPA.³⁹

Clinical Features

The most frequently reported clinical sign in COPD patients with IPA is a nonspecific antibiotic-resistant pneumonia associated with exacerbated dyspnoea.¹ The analysis from a large database on ICU patients with *Aspergillus*-positive cultures confirmed these data (*Asp*ICU project, data on file⁴). Indeed, depending on the algorithm used, 52 to 68% of patients with IPA required invasive ventilation compared with 2 to 24% of the patients considered to be merely colonized by the organism.

Patients' characteristics and clinical features reported in the largest review on COPD patients suffering from IPA are summarized in ►Table 2. At hospital admission, 77% of patients were receiving corticosteroids (including inhaled

Table 2 Patients characteristics¹

Number of patients: 56		
Sex	Male	42 (75%)
	Female	14 (25%)
Age (y)	Mean (±SD)	65.5 (9.3)
	Median (IQR)	66 (57–73)
Steroid treatment	At admission	43
	• Systemic use	40
	• Inhaled only	3
	At hospital (systemic use)	49
	None	2
	NA	5
Clinical signs (total points available)	Antibiotic-resistant pneumonia (56)	53
	Dyspnoea exacerbation (48)	48
	Wheezing increase (28)	22
	Fever > 38°C (39)	15
	Hemoptysis (12)	5
	Parietal pain	4 reports
Tracheobronchitis during bronchoscopy (33)		6
Duration between symptoms and diagnosis	Mean (±SD)	12.5 days (±11.3)
	Median (IQR)	8.5 days (6–16.5)
Ventilation	Invasive	43
	Noninvasive ventilation	1
	None	10
	NA	2
Total leucocytes	<12,000	10
	>12,000	30
	NA	16
Outcome	Death	53 (= 95%)
	Survival	3 (= 5%)

Abbreviations: IQR, interquartile range; NA, not available; SD, standard deviation.

Note: A total of 43 patients received treatment.

forms); this rate amounts to 96% during hospitalization. The evolution of symptoms is characterized by an improvement of the respiratory signs followed by an iterative recrudescence of the dyspnea,^{15,17} featured by a predominant bronchospastic component.^{1,12,40} In contrast to hematological patients,⁴¹ fever, chest pain, and hemoptysis were less often encountered in the COPD population.¹² These data were subsequently supported by a large database⁴ of ICU COPD patients (*Asp*ICU project, data on file).

It takes a median of 8.5 days between onset of IPA-related symptoms and diagnosis. This long delay may have contributed to the high rate of need for invasive ventilation (77% of patients).¹

Although nonspecific, an elevated white blood cell count higher than 12,000/mL was described in 75% of patients as well as thrombocytopenia ($<100,000$ platelets/mm³) in the late course.¹⁵ On the other hand, frequently used markers, such as C-reactive protein, procalcitonin, fibrinogen, and lactate dehydrogenase, are not systematically raised and therefore offer no discrimination.

Consequently, the optimal way to diagnose IPA in COPD remains to be determined especially when the patients are intubated and mechanically ventilated. Indeed, surgical lung biopsy might be contraindicated due to coagulation disorders and/or severe respiratory failure,^{42,43} precluding the possibility to prove IPA. To date, three algorithms have been published to diagnose IPA: one is specific for COPD,¹ whereas the two others are more generic (Clinical⁸ and EORTC/MSG⁶ algorithms). But the latter has been validated only in immunocompromised patients; however, ICU COPD patients only fulfill the classic host factor criteria with the EORTC/MSG algorithm when exposed to corticosteroid therapy for a prolonged period of time, defined as 0.3 mg/kg/d of prednisone equivalent for >3 weeks.^{6,44} Blot and colleagues have reported that the Clinical algorithm detects a greater proportion of the disease burden in ICU patients compared with the EORTC/MSG criteria mainly because host factors were often lacking in ICU patients.⁴ A recent study on a large ICU COPD population confirmed that more IPA cases were detected with the Clinical algorithm as compared with the EORTC/MSG criteria ($p = 0.013$).⁹ As the definitions for proven IPA are equal, the observed differences lie within the chosen diagnostic approach. Indeed, for both COPD and EORTC/MSG algorithms, several patients could not be classified: for the former because only Global Initiative for Chronic Obstructive Lung Disease (GOLD) III or IV could be considered as probable IPA, and for the latter as COPD is not recognized, in itself, as a relevant host risk factor. In addition, concordance between algorithms was assessed in 23 patients with histological data. A correct diagnosis (true positive + true negative) was more often obtained with the Clinical followed by the COPD and finally the EORTC/MSG algorithm (19, 12, and 3).⁹ Finally, analyzing the eight patients in whom IPA was discovered only after death, the Clinical, COPD, and EORTC/MSG algorithms classified them as putative/probable IPA in 7, 4, and 0 of the cases, respectively. Another insight from the AsplCU study is that GOLD II classified COPD patients under corticosteroids could be subject to developing IPA.^{9,40}

Therefore, in severe steroid-dependent COPD patients, the presence of a dyspnoea exacerbation and poor clinical status, despite broad-spectrum antibiotics and high doses of steroids, is highly suggestive of IPA, especially when a recent pulmonary infiltrate appears on chest X-ray and/or when *Aspergillus* species is retrieved in the sputum.

Hence, among COPD patients admitted to ICU, the Clinical algorithm seems to be more useful to diagnose IPA. The COPD algorithm is less appropriate due to the number of inconclusive diagnoses in particular for GOLD II COPD patients. IPA

should be considered in COPD patients, regardless of the GOLD stage, on chronic corticosteroid therapy with *Aspergillus* isolation, respiratory failure, and abnormal chest X-ray, especially after broad-spectrum antibiotic therapy. When IPA is probable and hence not yet confirmed, additional investigations must be undertaken to confirm the infection and treatment should be formally taken into account.

Diagnostic Procedures

Sputum

The exact incidence of airway colonization by *Aspergillus* spp. in the COPD population remains to be determined,^{45–48} but a recent report suggested an incidence of 78% of their patients.¹² Nevertheless, as pointed out above, when faced with antibiotic-resistant pneumonia, a positive culture for *Aspergillus* spp. must alert the physician.

Direct examination for *Aspergillus* spp., readily accessible as sputum production is generally increased in the case of IPA, is positive in 48% in this context.⁴⁹ Using the fluorescence techniques, positivity may increase up to 88%.⁵⁰ Although, in COPD patients, the presence of *Aspergillus* does not ascertain IPA diagnosis, it must raise the suspicion of IPA particularly when a pulmonary infection proves unresponsive to antibiotics, but not exclusively in the case of corticosteroid therapy. Repetitively positive cultures are even more indicative of infection,^{51–53} even if bacteria are cultured, which is often the case.¹ Nonetheless, the issue of diagnostic performance of sputum analyses remains debated in the literature.¹ The explanation could be that colonization may reflect a transitory passage of *Aspergillus* in the tracheobronchial tree, a prolonged but benign carriage, but also a necessary first step prior to invasive disease (as the incubation period before IPA is not determined).⁵⁴ Yet, the physician should keep in mind that an IPA may be present even in the absence of a positive culture for *Aspergillus*.¹

Serology

To date, the galactomannan (GM) antigen test (ELISA test, Platelia) is the most common diagnostic test used in clinical practice and predominantly studied in hematological cancers. One of the main interests lies in the fact that diagnosis could be obtained before the appearance of clinical signs,^{55,56} if blood samples were taken at least twice weekly with an optical density index (ODI) set to 1. However, other authors did not confirm these results.^{57–59} A recent meta-analysis reviewed numerous studies evaluating the performance of the test.^{60,61} Some noted that the discrepancies are due to the number of tests performed per week, the definition of IPA used or analyzed populations, running antifungals, as well as the ODI cutoff chosen. In the above-mentioned meta-analysis including 5,660 immunocompromised patients (mostly hematological, 586 with proven or probable IA, and using an ODI cutoff of 0.5), the sensitivity was 82% (95% confidence interval [CI]: 73–90%) and the specificity was 81% (95% CI: 72–90%).⁶¹

Few studies specifically assessed antigenemia in critically ill COPD patients suspected to have IPA. Despite several biases and with an ODI set to 0.5, the sensitivity was reported to be

between 11 and 91% and the specificity 66 to 100%.^{44,62–64} It has been suggested that the GM test was more efficacious in the hematological population as GM is not cleared by leucocytes unlike in the case of nonimmunocompromised individuals.

Again, data from hematological patients suggest that an increase in antigenemia of 1.0 within the first week could denote a progression of the infection which could be even more relevant for diagnosis than one value above the normal level.⁶⁵ In addition, even if the therapy is active, pulmonary lesions secondary to *Aspergillus* spp. may grow on computed tomography (CT) scan up to 2 weeks after the start of treatment,⁶⁶ thus, an increase of antigenemia could suggest a treatment failure inciting a change in antifungal therapy.

Nonetheless, despite some encouraging results, and specifically in COPD population, no decrease in mortality has been reported. Additional factors could also complicate the interpretation of the Platelia test: antifungals could reduce the sensitivity of the test,⁶¹ some cross-reactive antigens from foods and other intestinal fungi or bacteria could falsely positivate the GM analysis,^{67,68} or the simultaneous intravenous (IV) administration of piperacillin-tazobactam or amoxicillin-clavulanate⁶⁹ or plasmalyte.⁷⁰ For the latter, new products cross-react less with the assay.⁷¹

Next to serologic tests, polymerase chain reaction (PCR) analyses and dosage of plasma concentration of β -D-glucan, a component of the fungal cell wall, are available. In a meta-analysis, Cruciani et al reported a mean sensitivity of 80.5% (95% CI: 73.0–86.3) and a mean specificity of 78.5% (95% CI: 67.8–86.4) with one PCR dosage to diagnose IPA.⁷² When two consecutive positive tests are used, the mean sensitivity was 58.0% (95% CI: 36.5–76.8) and the mean specificity was 96.2% (95% CI: 89.6–98.6). To interpret these results, caution is required: definitions of IPA vary between studies, molecular methods are not standardized, plasma products could inhibit PCR testing, and the influence of previous antifungal exposure is unknown but a priori less sensitive to treatment pressure. Moreover, as the patients reported in the meta-analysis primarily suffered from hematological diseases, results could not be generalized particularly to COPD individuals where the difference between *Aspergillus* colonization and IPA is crucial but not robust enough with PCR. The detection of β -D-glucan in the plasma does not seem to be superior to determination of blood GM.⁷³

Radiology

Related IPA radiological findings in COPD patients are quite different compared with the ones observed in hematological patients. Where nonspecific consolidations (►Figs. 1 and 2) are the rule in the COPD patients,^{1,9,12,40} more suggestive images could be also seen but are specifically described in the hematological patients, such as the wedge-shaped consolidation (►Fig. 3), nodules (►Fig. 4), “halo sign” (►Fig. 3; better seen on thoracic CT scans), and “air-crescent sign” (►Fig. 5); the latter two being nearly pathognomonic of IPA in neutropenic hematological patients. In contrast, in COPD individuals, a normal chest X-ray virtually excludes IPA probably because pneumonia was diagnosed tardily as



Fig. 1 Chest X-ray showing bibasal nonspecific consolidations.



Fig. 2 Chest CT scan revealing bibasal nonspecific consolidations. CT, computed tomography.

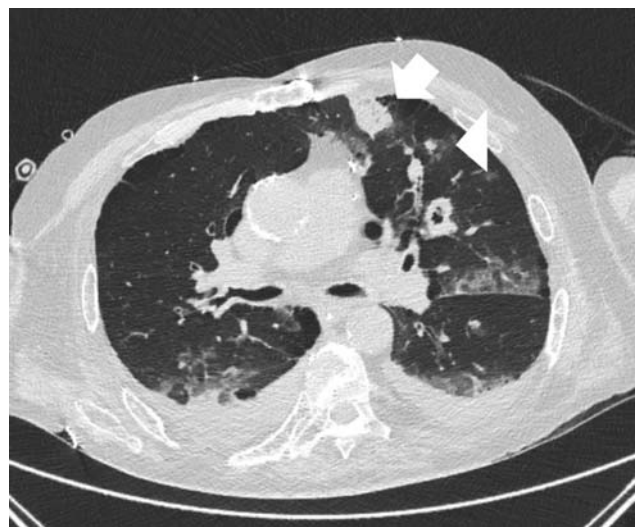


Fig. 3 Chest CT scan showing wedge consolidation (arrow) of the left upper lobe corresponding to an infarcted zone, and one nodule with the “halo sign” (arrowhead). CT, computed tomography.

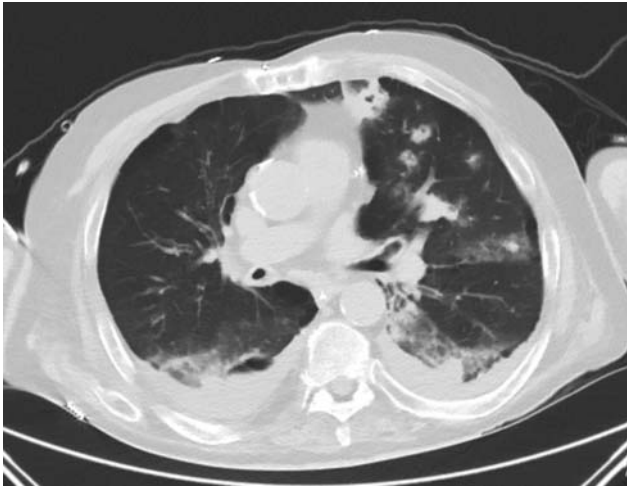


Fig. 4 The chest CT scan showing multiple nodules. CT, computed tomography.



Fig. 5 Chest CT scan showing a nodule with the “air-crescent sign”: infarcted tissue surrounded by an air-filled space (arrow). CT, computed tomography.

suggested by the high number of respiratory failure and intubation rate in patients suffering from IPA.⁹ Interestingly, on thoracic CT scan, wedge-shaped infiltrates, although rare, were nearly pathognomonic for IPA but did not reach statistical significance. Albeit more common, well-shaped nodules were particularly described in COPD patients with putative IPA (AspICU data on file⁴). Again, in a hematological population, Caillot et al showed that promptly performed thoracic CT scan, as it detects pulmonary lesions earlier than chest X-rays, could improve survival.⁵

To avoid misdiagnosis, the clinician must keep in mind that nodules can have infectious as well as noninfectious origin such as malignancy.

Fiberoptic Bronchoscopy

Not every patient can provide sputum for conclusive analysis. To alleviate this, fiberscopy could be performed to obtain endotracheal aspirate, bronchoalveolar lavage (BAL), bronchial washings, or brushing specimens for culture. Reported endotracheal aspirate culture yields were 46 to 77%,^{1,38,60} with a lower

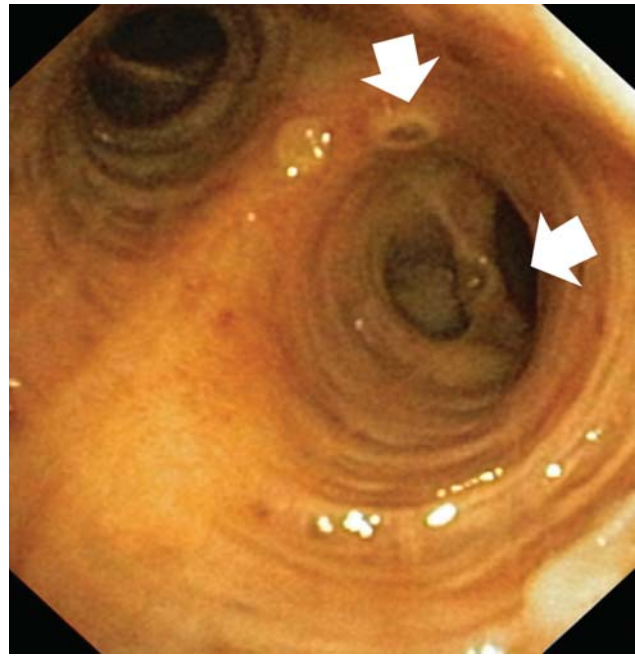


Fig. 6 Endoscopic view of the left bronchus showing mucosa covered by few ulcerations, some with blackish center (arrow).

sensitivity in patients on antifungals.⁷⁴ BAL was more often positive when prolonged pneumonia or extensive involvement of the pulmonary parenchyma was present. Interestingly, cytological scrutiny seems to be even more positive than cultures.^{8,53} It remains that a positive microscopy for *Aspergillus* alone could not absolutely distinguish colonization from infection. Currently, the detection of GM in BAL fluid is recommended to diagnose IPA⁷⁵ using a cutoff index of 0.5, with a sensitivity and specificity of 87% (95% CI: 0.79–0.92) and 89% (95% CI: 0.85–0.92), respectively.^{62–64,74,76}

However, whereas serum enzyme-linked-immunosorbent serologic assay (ELISA) could be performed without lung infiltrates, BAL could only be performed in cases of abnormal chest imaging and could not be repeated every day. Therefore, the ELISA test on serum can be more useful. In addition, usefulness of PCR tests on BAL fluid is still unknown as standardization is still lacking and due to their high sensitivity difference between infection and colonization cannot always be determined.⁷⁷ Whatever, the Avni et al's meta-analysis reported a sensitivity of 90.2% (95% CI: 77.2–96.1) and a specificity of 96.4% (95% CI: 93.3–98.1).⁷⁴

Beyond the realization of culture, antigenic tests, and PCR, performance of flexible bronchoscopy could detect some mucosal lesions enabling biopsies (→ Fig. 6), allowing diagnosis in 47% of the cases.¹ Additionally, transbronchial lung biopsies can be executed but their efficacy only is around 25%.¹ Regrettably, flexible bronchoscopy cannot always be performed in COPD patients due to their reduced lung status or function.

Lung Biopsy

As stated previously, IPA can only be ascertained by histology. The ways to obtain lung biopsies are through fiberscopy (bronchial or transbronchial specimen) and, more classically,

by open lung biopsy (OLB). Moreover, OLB may be of therapeutic interest by itself as pulmonary resection may be curative⁵ (see Surgical Treatment section). However, as lung function could be severely altered in COPD patients, surgery may be impractical. Although lung biopsy could be achieved via a percutaneous needle, with a success rate of around 50% (thus negativity does not exclude IPA), only peripheral lesions are concerned but in COPD individuals the likelihood of pneumothorax is increased.¹

While definitive confirmation of infection requires biopsy, immediate initiation of antifungals should be considered when IPA is suspected, lung biopsies being reserved for unconvincing cases.

Therapy

The data on treatment efficacy came mainly from hematological population thus are extended to COPD patients in the absence of dedicated studies. On this basis, when IPA is suspected, antifungals will be started without delay if compatible lesion(s) are detected on thoracic CT scan.⁴¹ At the same time, if exposed to steroids, they will be lessened, or even stopped, to the smallest possible dose as steroids have been described as a risk factor to develop IPA.

Curative Treatments

Nowadays, amphotericin B deoxycholate (AmB-d) and itraconazole are no longer recommended as treatment against IPA. The former due to its related toxicity, mainly as at least 30% of patients are exposed to renal failure, and the second because of associated drug interactions and poor bioavailability. Furthermore, studies have demonstrated a better efficacy of more recent antifungal compounds.⁷⁸

Nowadays, voriconazole (VRC) is the antifungal of choice because it is the most studied and the most effective one.^{78,79} A larger study comparing VRC (two IV doses of 6 mg/kg on day 1 then 4 mg/kg/12 h for at least 7 days, followed by 200 mg/12 h orally) against AmB-d (intravenously 1–1.5 mg/kg/d) in a randomized, unblinded trial that enrolled 277 patients reported a survival rate at 12 weeks of 70.8 vs. 57.9% ($p = 0.02$) with a better tolerance of VRC.⁷⁸ Another advantage is that VRC is available in IV and oral forms. However, its usage may be limited due to numerous drug interactions and side effects, mainly visual changes (8–69%, such as blurred vision, altered visual or color perception, and photophobia) and skin reactions (1–19%).^{79–81} In addition, an increase in liver enzymes was observed in 4.3 to 26.5% of patients, but returned to normal at termination.^{79,80} In the case of hepatic toxicity, it is important to exclude if the patient is part of the “poor metabolizer” population (genetically the activity of the CYP2C19 is low in 20% of non-Indian Asians, consequently VRC blood levels may be up to four times higher than that the in “normal metabolizer” population). Due to accumulation of cyclodextrin (the IV VRC vehicle) when creatinine clearance is less than 50 mL/min, the oral route is recommended, if possible, as no adjustment in the dosage is necessary.⁸⁰ For patients with moderate liver disease, the loading dose will be the usual but the following

doses will be halved.⁸⁰ No safety data are available in the case of severe hepatic impairment.

Other triazoles (Posaconazole, Isavuconazole) are now available but their use against IPA is less documented and even more in the COPD population. However, they have fewer side effects so may replace VRC notably when liver enzymes increase.^{82–84}

Lipid formulations of amphotericin B (liposomal amphotericin B [AmBisome], amphotericin B lipid complex [Abelcet] and amphotericin B colloidal dispersion [Amphotec]) have been developed to lessen AmB-d-related renal insufficiency. In addition, less hypokalemia, fever, and infusion-related chills are encountered except with Amphotec.⁸⁵ Although they are often suggested when VRC is contraindicated, in the COPD population there is no evidence of their effectiveness and their cost remains expensive.

Echinocandins (Caspofungin, Micafungin, and Anidulafungin), another class of antifungals, show some efficacy to control IPA.^{86,87} The reported side effects of the drugs are scarce and the tolerance exhibits a favorable profile.⁸⁷ Another advantage of this antifungal class is that no dose adjustment is needed for age > 18 years, race, gender, renal impairment, or hemodialysis, although the dosage of 35 mg/d after a full loading dose is proposed when moderate hepatic insufficiency is present.

Despite an outcome improvement for patients under VRC,⁷⁸ IPA prognosis remains limited. Therefore, combination therapy was suggested either with VRC-echinocandin or lipid formulation of AmB-echinocandin.⁸⁸ The former is the most studied one; however, the available data remain rare and not convincing enough to recommend combination therapy at first-line treatment but may be used as a salvage regimen. The association between azoles and AmB is not indicated in view of in vitro studies showing some antagonism.⁸⁹

While some studies in hematological patients reported some efficacy of lung lesion resections,^{5,90} the transposition of these results in COPD patients is often precluded due to the poor respiratory status. Hypothetically, wedge resection, by preventing the functional defect, can be discussed in selected cases, but no recent study sustains this approach.

The place of immunomodulation (such as growth factors, interferon-G, leucocyte transfusion, or vaccination) is anecdotal in COPD individuals as immunodepression is not the *primum movens*.

Prophylactic Treatments and Prevention

In the COPD population, considering that IPA diagnosis continues to be difficult and present a calamitous prognosis, prophylactic treatment could be evoked but there are no consistent data to support its use despite some inputs from hematological patients.^{91,92}

For the same reasons, prevention measures may be of importance. Despite insufficient data to firmly recommend a strategy, it seems reasonable to advise the following:

- When the patient is hospitalized, avoid exposure to *Aspergillus* spp. by wearing a high-efficiency mask in the case of *Aspergillus* exposure, by cleaning the surfaces

to avoid dust accumulation, and by erecting sealed barriers during construction works.⁹³

- At home, the only proposition we can provide is to avoid exposure to known *Aspergillus* reservoirs (for instance, constructions, cellars or lofts, composts, etc.).

Prognosis

Collecting the data available for IPA in the COPD population until 2007, the mortality rate was 95%.¹ At that time, ICU admission did not seem to modify this poor prognosis.^{15,44,94} In contrast, in more recent databases, a mortality rate between 55 and 60% has been reported.^{4,40} The explanation of this discrepancy could be that physicians now identify COPD by itself as a risk factor to contract IPA. As a result, suggestive symptoms are identified more rapidly and thus appropriate antifungals are administered earlier. In addition, the availability of VRC, a more efficacious compound, could have modified the outcome (no VRC administered in the first reports).

Conclusion

Although COPD patients may be colonized by *Aspergillus*, its presence in airway specimens could be the first sign of IPA motivating the performance of diagnostic procedures to offer the maximum chance of successful therapy. The first clinical symptoms are often persistent bronchospasm and/or respiratory infection resistant to antibiotics. Thoracic CT scan is recommended as chest X-ray is less sensitive to demonstrate mild pulmonary modifications, especially at the beginning. Bronchoscopy is useful to ascertain IPA diagnosis as mucosal lesions could be observed allowing biopsies or to obtain GM dosage in the BAL. The place of serological tests in the serum needs further studies and could not be routinely recommended. The use of criteria from the Clinical algorithm has demonstrated its usefulness in diagnosing IPA. Particularly when the patient is critically ill, and to provide the maximum chance of cure, appropriate treatment should be initiated immediately as well as diagnostic procedures should be started if IPA is suspected. Nowadays, VRC is the first-line antifungal and lipid formulations of AmB are the second choice. It could be an added value if COPD patients treated chronically by corticosteroids were given advice to avoid environmental exposure to *Aspergillus* spp.

Conflict of Interest

None declared.

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