# REVIEW

# Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease

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**ABSTRACT: Aspergillus spp. cultured in specimens from the airways of chronic obstructive pulmonary disease (COPD) patients are frequently considered as a contaminant. However, growing evidence suggests that severe COPD patients are at higher risk of developing invasive pulmonary aspergillosis (IPA), although IPA incidence in this population is poorly documented. Some data report that COPD is the underlying disease in 1% of patients with IPA.**

**Definitive diagnosis of IPA in COPD patients is often difficult as tissue samples are rarely obtained before death. Diagnosis is therefore usually based on a combination of clinical features, radiological findings (mostly thoracic computed tomography scans), microbiological results and, sometimes, serological information.**

**Of 56 patients with IPA reported in the literature, 43 (77%) were receiving corticosteroids on admission to hospital. Breathlessness was always a feature of disease and excess wheezing was present in 79% of patients. Fever (>38°C) was present in only 38.5%. Chest pain and haemoptysis were uncommon. Six out of 33 (18%) patients had tracheobronchitis observed during bronchoscopy. The median delay between symptoms and diagnosis was 8.5 days. The mortality rate was high: 53 out of 56 (95%) patients died despite invasive ventilation and antifungal treatment in 43 (77%) of them.**

**In chronic obstructive pulmonary disease patients, invasive pulmonary aspergillosis currently carries a very poor prognosis. Outcome could perhaps be improved by more rapid diagnosis and prompt therapy with voriconazole.**

**KEYWORDS: Aspergillosis, chronic obstructive pulmonary disease, fungal infection, infection in chronic obstructive pulmonary disease, invasive pulmonary aspergillosis**

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The fungus Aspergillus can be found worldwide, with preferential tropism for humid soil. Although numerous species have been reported, few are pathogenic and *Aspergillus fumigatus* accounts for ~90% of human infections. Due to the high sporulating capacity of Aspergillus, normal air contains a concentration ranging 1–100 spores·m$^{-3}$ [1, 2]. As the conidia released in the air after Aspergillus sporulation are small enough (2–3 μm diameter) to reach the alveoli, the lung is the main organ to be affected by Aspergillus. The mycological characteristics of *A. fumigatus* have been extensively reviewed and, therefore, will not be discussed in the present review [2–4].

Although Aspergillus spp. cause various diseases in humans, such as allergic bronchopulmonary aspergillosis and aspergilloma, the present review will focus only on invasive pulmonary aspergillosis (IPA). IPA is well known to account for a large number of mortalities due to fungi in haematological and solid-organ transplant patients [5]. According to recent autopsy series, its incidence has grown over the last 20 yrs [6–8]; this is probably related to the increasing use of immunosuppressive and corticosteroid therapies in this patient population [9, 10].

More recently, several authors have reported the occurrence of IPA in chronic obstructive pulmonary disease (COPD) patients, most of whom, but not all, were receiving steroid treatment, with a very high mortality rate [11–16]. An early diagnosis therefore seems crucial to improve prognosis [17, 18]. Even if Aspergillus spp. colonise the airways without generating an infection [19, 20], it is critical to recognise at an

early stage the possibility of IPA in COPD, in particular in severe (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV) steroid-dependent patients. The present review addresses the epidemiology and pathophysiology of IPA in COPD patients. It further discusses the early clinical signs observed in these patients, as well as the available diagnostic procedures, in order to facilitate rapid recognition and appropriate treatment.

The following definitions are used in the subsequent text.

COPD ''is a disease state characterised by airflow limitation that is not fully reversible.'' This definition refers to the National Heart, Lung, and Blood Institute and the World Health Organization (NHLBI/WHO) workshop report [21].

GOLD classification refers to the definitions described in the NHLBI/WHO workshop report [22].

IPA is characterised by lung parenchyma invasion and necrosis due to Aspergillus spp.

Subacute IPA represents direct invasion of lung parenchyma by hyphal elements but with a slowly progressive cavitary lung disease.

Chronic pulmonary aspergillosis shows radiological signs of tissue destruction, but without evidence of hyphal invasion, with microbiological markers of Aspergillus infection.

The term tracheobronchitis is used when Aspergillus organisms invade the tracheobronchial tree. Subclassification exists from Aspergillus tracheobronchitis, with inflammation of the mucosa without invasion and with secretions containing Aspergillus spp., to more invasive bronchial aspergillosis, such as pseudomembranous tracheobronchial aspergillosis (consisting of necrosis and sloughing of the epithelium and pseudomembrane resulting from necrotic fragments and hyphal elements) and ulcerative tracheobronchial aspergillosis (manifesting as endobronchial plaque(s), nodule(s), or area(s) of ulceration and necrosis). Further description of the different definitions of disease due to Aspergillus can be found in HOPE et al. [23].

## EPIDEMIOLOGY

To date, the frequency of IPA in COPD patients has been poorly documented. Assessing the incidence of IPA in this population is not easy due to the lack of a consistent case definition and the absence of infection surveillance measures. Moreover, colonisation by Aspergillus spp. is often difficult to distinguish from IPA, particularly at an early stage. However, there is growing evidence to suggest that COPD patients are at risk of IPA. In a review of 50 studies, COPD was the underlying condition in 26 out of 1,941 (1.3%) patients with aspergillosis [24]. In one large study, 9% of 595 patients with invasive aspergillosis (IA) suffered from pulmonary disease, without distinguishing among respiratory disorders [25]. RODRIGUES et al. [26] reported that COPD patients contribute to 1% of all cases of IA in their institution.

Steroids are believed to play a role in the emergence of IA, and some authors have investigated the correlation between the daily dose of corticosteroids and the probability of developing IA. In a renal transplant population, an average dose of

$\geqslant 1.25$ mg·kg$^{-1}$·day$^{-1}$ of prednisone was the best predictor of subsequent IA [27]. Moreover, in haematological patients treated by peripheral blood or bone marrow transplantation, dosages $\geqslant 1$ mg·kg$^{-1}$·day$^{-1}$ prednisone during $\geqslant 21$ days were associated with a significantly greater risk of developing IA [28]. When all the data from the literature are pooled, >20 mg prednisone per day or a cumulative dose of >700 mg was associated with an increased risk of infectious complications [29].

Although precise dosages or durations of corticotherapy cannot be extrapolated from the literature, data support the fact that COPD patients are at risk for IPA when they have received high doses of corticosteroids or when steroids have been administered for a long time [11–13, 30]. Recently, some reports have suggested that high doses of inhaled corticosteroids may also be a risk factor for IPA [31–33]. Explanations as to how steroids may promote IPA are discussed later (see Pathophysiology section).

Despite the close relationship between steroids and IPA in COPD patients, it has been reported that some COPD patients may develop IPA without exposure to steroids [34]. Moreover, it has been reported that some infections, in particular viral infection, such as influenza [35, 36] or cytomegalovirus [9], may precede IPA, suggesting a role in causation [37].

## IPA DEFINITIONS

Until recently, no standardised definition of IPA was available. Following the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group consensus conference, common definitions for proven, probable and possible IPA were published for the highly susceptible population of immunocompromised patients with cancer and recipients of haematopoietic stem cell transplants [38].

In contrast, diagnostic criteria used in the literature so far for IPA in COPD patients are variable. Therefore, the present authors propose IPA definitions in that population of patients (table 1) in an attempt to standardise definitions, and based on the published information [12, 13, 34, 36–54], which are summarised in table 2.

## PATHOPHYSIOLOGY

Aspergillus spp. is an airborne pathogen and its spores are small enough (2–3 μm) to reach lung parenchyma via the airways. The majority of Aspergillus conidia are probably excluded from the lungs by the ciliary action of the bronchial epithelium. However, in COPD patients, ciliary activity is often impaired by tobacco smoke and multiple episodes of infection, as well as repeated epithelial damage. The impairment of the defence mechanisms of the airways facilitates the binding of conidia to the epithelial layer [3]. Consequently, Aspergillus spp. first invade the bronchial mucosa, then the adjacent pulmonary parenchyma, and finally the vasculature inducing secondary pulmonary infarction.

The second line of host defence is the phagocytic system [55]; it comprises the alveolar macrophages (AM) that play a prominent role in destroying the A. fumigatus conidia, and the neutrophils that kill hyphae and germinating spores [56–59]. Other immune cells, such as natural killer lymphocytes [60], and the innate pulmonary host defences also play a role in protecting individuals against IA [61, 62].

| TABLE 1 | Definitions of invasive pulmonary aspergillosis (IPA) in chronic obstructive pulmonary disease (COPD) patients |
|---|---|
| **Proven IPA** | Histopathological or cytopathological examination, from needle aspiration or biopsy specimen obtained from any pulmonary lesion present for <3 months, showing hyphae consistent with Aspergillus and evidence of associated tissue damage, if accompanied by any one of the following: <br> 1) Positive culture of Aspergillus spp. from any LRT sample. <br> 2) Positive serum antibody/antigen test for *A. fumigatus* (including precipitins). <br> 3) Confirmation that the hyphae observed are those of Aspergillus by a direct molecular, immunological method and/or culture. |
| **Probable IPA** | As for proven IPA but without confirmation that Aspergillus is responsible (points 1, 2 and 3 are not present or tested). <br> OR <br> COPD patient, usually treated with steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea[#], suggestive chest imaging[¶] (radiograph or CT scan; <3 months[+]) and one of the following: <br> 1) Positive culture[§] and/or microscopy for Aspergillus from LRT. 2) Positive serum antibody test for *A. fumigatus* (including precipitins). <br> 3) Two consecutive positive serum galactomannan tests. |
| **Possible IPA** | COPD patient, usually treated by steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea[#], suggestive chest imaging[¶] (radiograph or CT scan; <3 months[+]), but without positive Aspergillus culture or microscopy from LRT or serology. |
| **Colonisation** | COPD patient with positive Aspergillus culture from LRT *without* exacerbation of dyspnoea, bronchospasm or new pulmonary infiltrate. |

Data from references [23] and [38]. LRT: lower respiratory tract; *A. fumigatus*: *Aspergillus fumigatus*; GOLD: Global Initiative for Chronic Obstructive Lung Disease; CT: computed tomography. [#]: Exacerbation of dyspnoea and/or bronchospasm resistant to appropriate treatment including antibiotics; [¶]: pulmonary lesion(s) unresponsive to appropriate antibiotics (refers to dose, route, spectrum and activity against cultured bacteria); [+]: pulmonary lesions, especially cavitary, present for >3 months are better classified as chronic pulmonary aspergillosis (see text), unless direct tissue invasion is demonstrated; [§]: standard or sabouraud culture, or molecular detection test when licensed.

Mechanisms and sequence of the conidia destruction by AM have been extensively investigated, and include the following four steps. 1) Phagocytosis of conidia (a 2-h process), 2) swelling of conidia, followed by 3) killing of Aspergillus, beginning only 6 h after AM internalisation, and then 4) eradication of conidia, involving production of reactive oxidant intermediates (ROI) [63]. Neutrophils kill Aspergillus after adhesion to the fungal surface and production of ROI, as well as secretion of proteolytic enzymes from granules [2].

Steroids enhance the growth of some Aspergillus (especially *A. fumigatus*) [64] and decrease AM antifungal activity [65, 66] by inhibiting ROI production and, therefore, favour the emergence of IPA [63]. In addition, neutrophils are also inhibited by corticosteroids; this impairment can be prevented by granulocyte colony-stimulating factor and interferon (IFN)-γ [58, 67]. Furthermore, steroids suppress T-helper cell type 1 cytokine production, as well as enhancing Th2 cytokines, diminishing the host response against Aspergillus [68].

Histological studies compared IPA lesions in steroid-treated and neutropenic animals. In the former, the immune response is characterised by an important influx of neutrophils into the lung parenchyma and interleukin-10 production [59]; histological analyses demonstrate large foci of pneumonia, exudative bronchiolitis with bronchial and alveolar destructions, and haemorrhagic necrosis with neutrophil infiltration. In contrast, only a few Aspergillus are observed and are mostly in their nongerminated form when present [59, 69]. Thus, in comparison with neutropenic animals, steroid-treated animals seem to die from an excessive host response rather than from a fungal invasion. As pneumonia is the main lesion encountered during histological examinations, this could explain why, on chest radiographs, nonspecific consolidation is more frequently observed than multiple nodules in COPD patients undergoing steroid treatment (table 3).

Furthermore, in autopsy reports from COPD patients, disseminated aspergillosis is not a predominant feature, suggesting that haematological spread is rare (table 4). These findings are in accordance with results observed in animal models of IPA, where corticosteroid-treated animals exhibit a small index of extrapulmonary invasion compared with the chemotherapy-treated animals [59, 69].

Not only oral but also inhaled steroids might promote IPA in COPD patients. High doses of inhaled steroids therefore have potential systemic effects and could depress the adrenal function [70]. Although still debated, the use of inhaled steroids in COPD has been supported by preliminary results [71]. If these results are confirmed, the beneficial effects of widespread use of inhaled steroids in these patients, particularly the most severe, must be weighed against the risks of systemic side-effects (especially the effect on immunity).

Another concept could explain why some patients without the common risks of immunodepression contract IPA. In patients suffering from sepsis, the immune response is biphasic. The initial hyperinflammatory phase is followed by an anti-inflammatory response. When the latter reaction is excessive, it may lead to an immunoparalysis, also known as compensatory anti-inflammatory response syndrome. Consequently, the patient should be considered as temporarily immunocompromised and may be at risk of developing opportunistic infections, such as IPA [72].

## CLINICAL FEATURES OF IPA IN COPD
The main clinical sign in COPD patients with IPA is a nonspecific antibiotic-resistant pneumonia associated with exacerbated dyspnoea. Patients' characteristics and clinical

| TABLE 2 | Characteristics of the patient population |
|---|---|
| **Total number of patients** | 56 |
| **Sex** | |
| Male | 42 (75) |
| Female | 14 (25) |
| **Age yrs** | |
| Mean±SD | 65.5±9.3 |
| Median (IQR) | 66 (57–73) |
| **Steroid treatment** | |
| At admission | 43 |
| Systemic use | 40 |
| Inhaled only | 3 |
| In hospital (systemic use) | 49 |
| None | 2 |
| NA | 5 |
| **Clinical signs (total patients available)** | |
| Antibiotic resistant pneumonia | 53 (56) |
| Dyspnoea exacerbation | 48 (48) |
| Wheezing increase | 22 (28) |
| Fever >38°C | 15 (39) |
| Haemoptysis | 5 (12) |
| Parietal pain | 4 |
| Tracheobronchitis during bronchoscopy | 6 (33) |
| **Duration between symptoms and diagnosis days** | |
| Mean±SD | 12.5±11.3 |
| Median (IQR) | 8.5 (6–16.5) |
| **Ventilation** | |
| Invasive | 43 |
| Noninvasive ventilation | 1 |
| None | 10 |
| NA | 2 |
| **Total leukocytes** | |
| <12000 | 10 |
| >12000 | 30 |
| NA | 16 |
| **Outcome**[¶] | |
| Death | 53 (95) |
| Survival | 3 (5) |

Data are presented as n or n (%), unless otherwise stated. Data from [12, 13, 34, 36, 37, 39–54]. IQR: interquartile range; NA: not available. [¶]: A total of 43 patients received treatment.

| TABLE 3 | Number of patients[#] with radiological signs |
|---|---|
| **Chest radiographs** | |
| Nonspecific consolidation | 36 |
| Specific images | 10 |
| Nodules | 3 |
| Cavitation | 3 |
| Wedge consolidation | 3 |
| Round consolidation | 1 |
| No infiltrate | 2 |
| NA | 8 |
| **Chest CT scan** | |
| Contributive | 11 |
| Halo sign | 1 |
| Nodule + cavitation | 2 |
| No description | 8 |
| Noncontributive | 5 |
| Not done | 40 |

Data from [12, 13, 34, 36, 37, 39–54]. NA: not available; CT: computed tomography. [#]: total n=56.

fever. Moreover, again in contrast to symptoms associated with IA in haematological patients, chest pain and haemoptysis were rarely described in COPD patients. Tracheobronchitis was observed in six out of 33 patients who underwent bronchoscopy (table 2).

The onset of symptoms occurred with a median of 8.5 days before IPA diagnosis (table 2). During hospitalisation, invasive ventilation was required in 43 patients. This high incidence could be due to the long delay between the beginning of the disease and diagnosis.

Laboratory results revealed an elevated white blood cell count >12,000 cells·mL$^{-1}$ in 30 out of 40 patients (table 2). Inconsistently, other parameters, such as C-reactive protein, fibrinogen and lactate dehydrogenase, may also increase. Thrombocytopenia (<100,000 platelets·mm$^{-3}$) was frequently observed in the late course [12].

Therefore, in severe steroid-dependent COPD patients, the presence of a dyspnoea exacerbation and poor clinical status, despite the use of broad-spectrum antibiotics and high doses of steroids, is highly suggestive of IPA, especially when a recent pulmonary infiltrate appears on chest radiograph and/or when Aspergillus species is retrieved in the sputum. In the case of a high-probability, but not confirmed, IPA, a diagnostic procedure must be performed to confirm the presence of the disease and treatment should be strongly considered.

## DIAGNOSTIC PROCEDURES
### Sputum
Although COPD patients may be colonised with Aspergillus spp., studies to ascertain this finding are scarce and, consequently, further investigations are needed to evaluate the true incidence of airways colonisation in this patient population [19, 20, 77, 78]. Nevertheless, the presence of Aspergillus spp. in the sputum must not be trivialised, especially in cases of antibiotic-resistant pneumonia.

features reported in various studies in the literature are summarised in table 2 (only studies with sufficient data are included in this analysis). At the time of hospital admission, 43 patients (77%) were treated with steroids, including three receiving only inhaled forms of steroids. When considering the hospital stay, corticosteroids were administered in 96% of patients (49 out of 51). Multiple episodes of breathlessness are characteristic of the infection, and these exacerbations often occur after initial improvement of the respiratory symptoms [12, 30]. A significant bronchospastic component is documented in 79% of patients when reported. As described in the literature [73–76], fever is present in only 38.5% of patients (15 out of 39), contrasting with the findings in haematological patients where fever is the most common sign (87%) [74]. High-dose corticotherapy could account for the absence of

| TABLE 4 | Diagnostic procedures |
|---|---|
| **Positive cultures** | |
| Sputum | 19 |
| Endotracheal aspirate | 29 |
| Bronchoalveolar lavage | 12 |
| Protected brush specimen | 6 |
| Pleural fluid | 1 |
| Lesion brushing | 1 |
| Bronchial washing | 1 |
| **Antigenaemia**[#] | 12 out of 25 |
| **Positive Aspergillus antibodies** | 2 |
| **Positive biopsy** | |
| Transbronchial lung biopsy | 6 |
| Open lung biopsy | 1 |
| Bronchial | 2 |
| Not detemined | 1 |
| **Autopsy (30 patients)** | |
| Invasive pulmonary aspergillosis | 24 |
| Disseminated aspergillosis | 6 |
| **Pathogens** | |
| Fungus | |
| *A. fumigatus* | 43 |
| *A. niger* | 2 |
| Aspergillus spp. | 2 |
| *A. fumigatus + A. flavus* | 3 |
| *A. flavus* | 1 |
| NA | 5 |
| Other pathogens reported | 36 |

Data from [12, 13, 15, 34, 36, 37, 39–54]. A.: *Aspergillus*; NA: not available.
[#]: Reported in reference [15] only.

Since mucus hypersecretion is a hallmark in COPD patients, sputum examination is often available. Moreover, its production is usually increased in IPA. Direct examination of the sputum for Aspergillus spp. can be rapidly performed and its positivity reaches 48% in case of IPA [79]. This yield may be increased up to 88% by the use of fluorescence techniques [80]. Although Aspergillus could grow on common culture medium, the Aspergillus growth is better on specific fungal medium. Positive sputum culture for Aspergillus is not diagnostic *per se* of IPA but should raise the suspicion of infection when the patient, especially when on steroid treatment, does not respond to antibiotics. Repeatedly positive cultures are even more suggestive of infection [81–83]. Aspergillus spp. is often retrieved with other pathogens (table 4) and, therefore, is then falsely considered as a contaminant. Although FISHER *et al.* [84] demonstrated the poor utility of respiratory cultures for IPA diagnosis in a population where >85% patients were suffering from haematological disease, these results were not confirmed by others [15, 20, 81, 85]. By contrast, in another study [86], Aspergillus spp. were isolated in 477 patients with ''underlying pulmonary disease'' (without other specification); among these, IA was diagnosed in 45 patients.

It remains unclear why some patients are only colonised by Aspergillus while others develop IPA without positive

sputum. Colonisation may correspond to a temporary passage of Aspergillus in the tracheobronchial tree, a long-term benign carriage, or the sign preceding invasive disease (as the incubation period before IPA is unknown) [23]. In contrast, the absence of positive sputum culture during IPA may be due to the low sensitivity of the diagnostic method [79], the presence of only few Aspergillus and mostly in their nongerminated form in the lesions [59, 69], or the tendency of Aspergillus to invade the vessels and to induce lung infarction [3]. Finally, as COPD definitions vary between reports [87], comparisons between studies are difficult and therefore no conclusions can be drawn.

### Serology

The current galactomannan (GM) antigen test (ELISA test, Platelia® Aspergillus; Sanofi Diagnostics Pasteur, Marnes-La-Coquette, France) has sensitivity in the range of 1 ng·mL$^{-1}$ [88]. The ELISA test was used particularly in haematological malignancies, in which it demonstrated a benefit as the diagnosis could be achieved before the appearance of clinical signs [75, 89]. Thus, antigenaemia preceded fever, positive chest radiograph, high-resolution pulmonary computed tomography (CT) scan, and the first positive culture results by a median of 3.5, 8, 6 and 9 days, respectively [75]. To obtain such results, blood samples must be taken at least twice per week and the optical density index set to 1. However, these results were not confirmed by others [90–92], and some authors even reported sensitivity as low as 29.4% [93]. In a multicentre study, sensitivity and specificity were found to be 50 and 97%, respectively, and only one-third of the patients had a positive antigen response before IPA diagnosis on CT scan [74]. Another group reported that although the sensitivity was 82.5% in 40 bone marrow-transplant recipients with proven or probable IPA, the ELISA test was also positive in 31 of 169 patients without any sign of infection [94]. These discrepancies are probably due to the number of tests performed per week, the definition of IPA used (sometimes with the inclusion of ''possible'' IPA) and the optical density index cut-off chosen [75, 89, 90, 93–98]. There are other explanations that have been reviewed recently [99].

More recently, antigenaemia was tested in critically ill COPD patients with suspected IPA. Among 25 patients tested, 12 were positive (48%); however, no firm conclusions could be drawn due to the small sample size, the retrospective design of the study, the lack of a systematic policy of sampling and the absence of a search for confounding factors [15].

Interestingly, an increase in antigenaemia over a baseline value may be even more of a discriminant than a single value above the normal level. Indeed, in allogenic stem cell-transplant recipients, BOUTBOUL *et al.* [100] demonstrated that a raise in antigenaemia of 1.0 over the baseline value during the first week of observation was associated with progressive disease (sensitivity and specificity of 44 and 87%, respectively, and a positive predictive value of 94%). As the pulmonary lesions caused by Aspergillus spp. usually increase on CT scan up to 2 weeks after diagnosis [101], even on effective treatment, it is difficult to conclude that the treatment fails on the sole argument of imaging. Thus, a rise in antigenaemia provides an argument for unsuccessful treatment and, hence, 1 week could be gained for changing the therapy.

The Platelia® test has several limitations. First, the main interest of an earlier diagnosis is to improve survival rate by enabling prompt and appropriate treatment to be initiated. However, despite interesting results, no prospective study has shown a mortality reduction by using the antigen test. Secondly, false-positive results have been reported in patients receiving piperacillin/tazobactam or amoxicillin/clavulanate [102–105]. Therefore, in patients treated with these antibiotics, antifungal therapy must be reconsidered if the only clues to support IPA diagnosis are repeatedly positive GM Platelia® tests. Thirdly, cross-reactions have been described with other fungi, bacteria, cyclophosphamide and food [103, 106–108]. Finally, it is unknown whether the results observed in haematological malignancies could be extrapolated to patients with other underlying diseases, such as COPD.

In addition to serological tests, other blood analyses are under development, including PCR tests and dosage of plasma concentration of the β-D-glucan. Preliminary results suggest that PCR has a good sensitivity and specificity [109–111]. However, there are no standardised methods, definitions of IPA vary between studies and caution is needed because plasma products could inhibit PCR testing [112]. The determination of plasma concentration of the β-D-glucan, a component of the fungal cell wall, does not appear to be superior to GM blood tests [113, 114].

Finally, as the antibody response is often weak in patients on long-term steroid therapy, the usefulness of antibodies against Aspergillus in IPA may be less sensitive than in immunocompetent patients. Moreover, the course of acute IPA is too fast to elicit an antibody response. In contrast, this is an extremely useful technique in patients with chronic pulmonary aspergillosis. Patients with COPD have a relatively normal immune system compared with neutropenic or bone marrow-transplant patients and are therefore likely to generate antibodies. While this area clearly needs substantial additional work, the presence of antibodies against Aspergillus and particularly seroconversion in the right clinical context with or without the presence of Aspergillus in sputum, might contribute to making a diagnosis of IPA in this type of patient [115]. Further information on this topic appears in a recent review of laboratory diagnosis of IA [116].

### Radiology

Chest radiographs may be normal in the early stages of IPA. When present, multiple radiological signs have been described as being associated with IPA, such as consolidation (figs 1 and 2), nodules (fig. 2), the ''halo sign'' (fig. 3; better seen on thoracic CT scans) and the ''air-crescent sign'' (fig. 2). The latter two signs are almost pathognomonic of IPA in neutropenic haematological patients. The halo sign corresponds to a low attenuation surrounding a mass or nodule [117, 118], and the air-crescent sign is related to the contraction of infarcted lung tissue delineated by an air-filled space [118]. Although these signs are well described during neutropenia, it seems they are less frequently observed in COPD and solid organ-transplant patients [119, 120], where nonspecific consolidations are seen more frequently than the specific features mentioned in table 3. The excessive host response (see Pathophysiology section), the lung parenchyma changes secondary to the underlying disease or the delay before the

diagnosis, as reported in haematological patients [101], may explain why radiological findings are less specific in COPD patients. CAILLOT et al. [18] showed that survival can be improved when a thoracic CT scan is performed at the beginning of the disease, because it is far more sensitive than standard chest radiographs for detecting early lesions. In another study, thoracic CT scan abnormalities preceded, respectively, chest radiograph by 4.7 days, latex agglutination by 7.1 days and β-D-glucan measurements by 11.5 days [113].

An important issue remains: to exclude a cancer lesion when a nodule is discovered on chest imaging. To facilitate the correct diagnosis, it may be useful to compare present chest imaging with previous chest imaging (if available) and to use common criteria for cancer, such as the presence of irregular and spicular borders. The physician in charge must also consider other potential infectious and noninfectious processes as part of the differential diagnosis.

### Fibreoptic bronchoscopy

When no sputum is available or contributive, material for culture should be obtained by fibreoptic bronchoscope (endotracheal aspirate, bronchoalveolar lavage (BAL), or bronchial washings or brushings). The yield of cultures has ranged 46–77% [73, 74, 79, 82, 85], while lower yields have been reported when patients were receiving high doses of antifungals [121]. BAL was more often positive in case of prolonged pneumonia or extensive pulmonary lesions. BROWN et al. [122] suggested that the positivity of BAL depends on the type of IPA: 20% in the angioinvasive form and 80% in the airway invasive form. Interestingly, cytological examination seems to be more often positive than cultures [79, 123].

In addition, antigen or PCR tests can be carried out on BAL fluid but standardisation is lacking. In one study performed in haematological patients using a latex agglutination test, sensitivity and specificity were 67% and 89%, respectively [74]. Although the ELISA antigen test on BAL fluid is feasible and reliable, the ELISA test on serum is probably more useful due to the repeatability of the method and the possibility of earlier diagnosis. BAL is only performed when pulmonary infiltrates are observed on chest imaging, while serum ELISA can be carried out before lung infiltrates are visible [124]. Although PCR on BAL fluid demonstrated poor specificity and standardisation, with 23% false-positive results [125, 126], other studies demonstrated a higher sensitivity and specificity, up to 100 and 100%, respectively [127–133]. Furthermore, PCR may be too sensitive, so that the difference between colonisation and infection can often be difficult to establish [134].

BAL-positive microscopy for Aspergillus is highly suspicious of active disease, although it is unable to definitively differentiate between colonisation and infection. While definitive confirmation of infection requires biopsy, immediate initiation of antifungals should be considered. During flexible bronchoscopy examination, some mucosal lesions might be present and thus biopsies can be obtained (fig 1). The yield of such biopsies has been reported to be as high as 47% in patients with proven or probable IPA [135, 136]. Furthermore, transbronchial lung biopsies can be performed (fig. 4) but the yield is ~25% [79, 135]. Unfortunately, despite its usefulness, performance of flexible bronchoscopy in COPD patients is
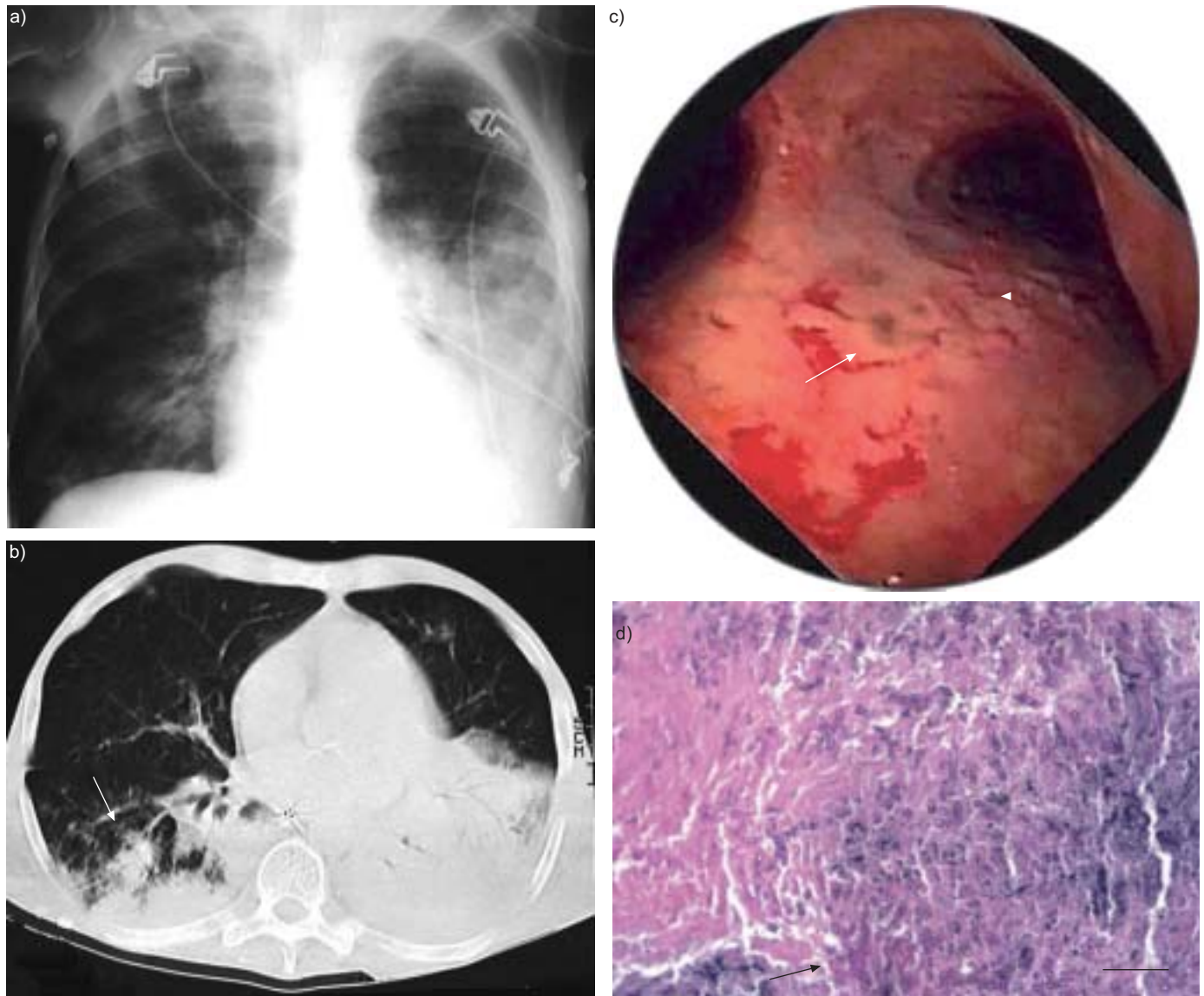
**FIGURE 1.** Successive procedures used to diagnose invasive pulmonary aspergillosis (IPA) in a 54-yr-old Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV patient. a) Chest radiograph showing nodular infiltrates in the right lower lobe and consolidation of the left lower lobe. b) Chest computed tomography scan performed on the same day revealing nodular lesions in the right lower lobe (arrow) and pneumonia of the left lower lobe. c) Endoscopic view of the trachea showing mucosa covered by diffuse nodular yellowish pseudomembranes (arrow) extending into the right major bronchus (arrowhead). d) Microscopic section demonstrating branching hyphae invading the depth of the infarcted tracheal mucosa (arrow). Scale bar=50 μm. Reproduced and modified from [12] with permission of the publisher.

sometimes difficult due to their poor lung status and function. Moreover, due to its poor yield, transbronchial lung biopsies must be performed only when the infection does not respond to adequate antifungal therapy.

***Lung biopsy***

As reported earlier, only histology can confirm IPA. Although transbronchial lung biopsies can provide lung tissue, the classical way to obtain parenchyma is through an open lung biopsy (by either classical thoracotomy or thoracoscopy). Nevertheless, in the COPD population, surgery is often precluded due to the poor lung function. In addition to its use as a diagnostic tool, lung resection may be therapeutic [18] (see section on surgical treatment).

Lung tissue can also be obtained by percutaneous needle biopsy, with a yield in the range of 50%; thus, negative results do not exclude the diagnosis [73]. Although percutaneous lung biopsy is particularly indicated for peripheral lesions [137], the risk of pneumothorax is of concern in COPD patients.

To enhance the chance to cure the patient, treatment should be started without any delay on the basis of a presumptive diagnosis alone. Lung biopsy should be performed when there is a doubt in the diagnosis of probable IPA.

Based on the current available data, and as the diagnosis of IPA is based on the results of several diagnostic tests, table 5 focuses on the combination of clinical features, radiological
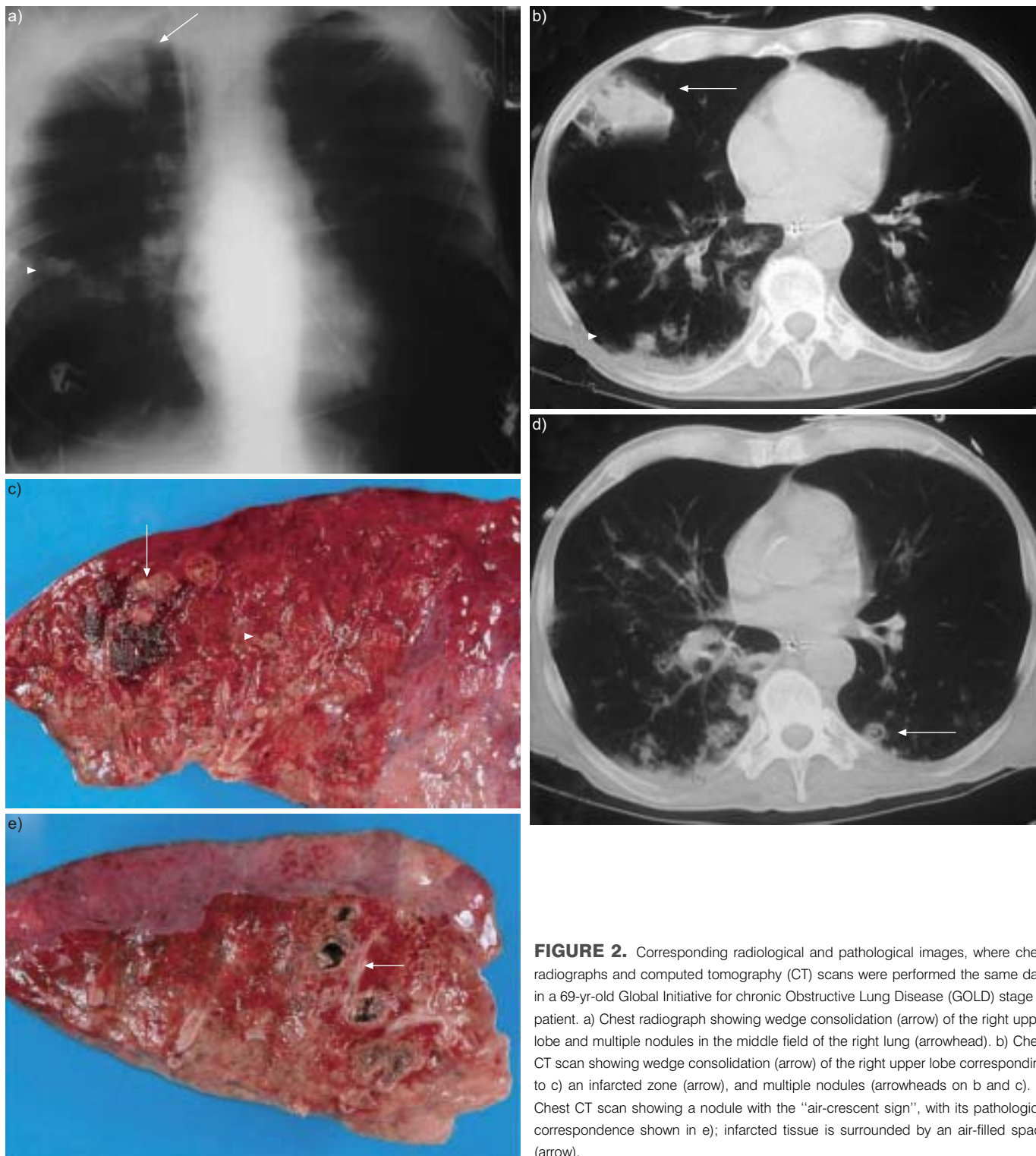
**FIGURE 2.** Corresponding radiological and pathological images, where chest radiographs and computed tomography (CT) scans were performed the same day, in a 69-yr-old Global Initiative for chronic Obstructive Lung Disease (GOLD) stage IV patient. a) Chest radiograph showing wedge consolidation (arrow) of the right upper lobe and multiple nodules in the middle field of the right lung (arrowhead). b) Chest CT scan showing wedge consolidation (arrow) of the right upper lobe corresponding to c) an infarcted zone (arrow), and multiple nodules (arrowheads on b and c). d) Chest CT scan showing a nodule with the ''air-crescent sign'', with its pathological correspondence shown in e); infarcted tissue is surrounded by an air-filled space (arrow).

findings, microbiological results and serological information to provide diagnostic certainty to guide physicians.

**THERAPY**

CAILLOT *et al.* [74] demonstrated that up to 82% of patients with IPA survived with a strategy aimed at reducing time to diagnosis and initiation of treatment. Although published data specific for COPD patients are lacking, it seems reasonable to recommend a thoracic CT scan as soon as IPA is suspected. In case of compatible lesion(s), treatment must be initiated promptly, followed by diagnostic procedures to better classify IPA (table 5).

**FIGURE 3.** A chest computed tomography scan showing probable invasive pulmonary aspergillosis in a 76-yr-old Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV patient. Multiple nodules can be seen, some with the ''halo sign'' (arrow).

Treatment administered to patients in the selected studies (see Clinical features of IPA in COPD section) is summarised in table 6. In view of these data, studies are needed to evaluate the efficacy of new antifungals in the COPD population.

In addition, doses of steroids, if present, must be reduced to as low a level as possible because high steroid dosages have been reported to be a risk factor for IPA [138].

### Curative treatments

Amphotericin B and itraconazole

Until recently, amphotericin B deoxycholate (AmB-d) was considered as the mainstay of therapy because of its broad antifungal activities and low cost, as well as its long-standing use in hospital. The recommended dosage is now 1 mg·kg$^{-1}$·day$^{-1}$, but may be increased to 1.5 mg·kg$^{-1}$·day$^{-1}$. Numerous side-effects limit its use, especially the high rate of renal failure. The renal impairment is dose-dependent, and with the high dosage, ⩾30% of patients will develop renal insufficiency.

Two different approaches were studied to decrease toxicities related to high dosage of AmB-d. First, continuous infusion, instead of administration over 2–6 h, was associated with a significant reduction of drug-related side-effects with similar efficacy [139, 140]. Yet, as fungal aetiologies were not clearly reported, implementation of these studies is limited.

Secondly, lipid formulations of amphotericin B (liposomal amphotericin B (AmBisome®; Gilead Sciences, Foster City, CA, USA), amphotericin B lipid complex (Abelcet®; Elan Pharma, Dublin, Ireland) and amphotericin B colloidal dispersion
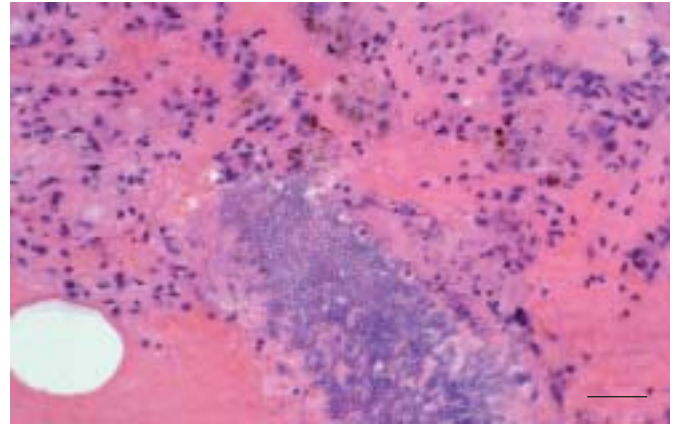


**FIGURE 4.** Histological confirmation of invasive pulmonary aspergillosis obtained by transbronchial lung biopsy in a 70-yr-old Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV patient. Scale bar=50 µm.

(Amphotec®; Ben Venue Laboratories, Inc., Bedford, OH, USA)) can replace AmB-d due to their superior renal safety. They induce fewer infusion-related chills and fever, except Amphotec® [141], and hypokalaemia is reported to occur less frequently in patients receiving lipid formulations than in those under AmB-d [141]. Treatment is often prolonged until 15 days after the disappearance of symptoms, with a possible relay with itraconazole. The major limitation of such treatments is related to cost. Administration of AmB-d in fatty-acid emulsion is contraindicated due to infusion-related toxicity and lack of efficacy [142].

Itraconazole is as effective as AmB-d in IPA patients [143, 144]. It has been suggested that itraconazole could be used whenever oral treatment is possible, while AmB-d is favoured when an intravenous route is required. The recommended dosage is 600 mg for 3 days to obtain a rapid plateau and then 400 mg·day$^{-1}$. The optimal duration of treatment is uncertain but may be as long as 6 months. The oral itraconazole solution has a better bio-availability than capsules and allows more stable blood levels. Serum concentration of itraconazole should be maintained at around 1,000 ng·mL$^{-1}$ for itraconazole and its derivatives (>250 ng·mL$^{-1}$ if itraconazole is only considered). An *i.v.* solution, approved by the Food and Drug Administration in 1999, is now available, albeit in only a few countries. In one prospective, open and multicentred trial, the efficacy and safety of *i.v.* (200 mg *b.i.d.* for 48 h, then 200 mg·day$^{-1}$ for 12 days) followed by oral itraconazole (capsules: 200 mg *b.i.d.*) were evaluated. A complete or partial response was observed in 48% (15 out of 31) of patients [145]. The main limitations of itraconazole use are related to its numerous drug interactions (including some benzodiazepines used in the intensive care unit for sedation), its poor bioavailability, as well as its negative inotropic effect that forces caution when administered to a patient suffering from cardiac heart failure or shock [146]. With the advent of new antifungal compounds, the use of itraconazole probably will be confined to consolidation therapy.

The efficacy of AmB-d, its lipid formulations and itraconazole in COPD patients is unknown.

| TABLE 5 | Diagnostic certainty of invasive pulmonary aspergillosis (IPA) in chronic obstructive pulmonary disease (COPD) patients | | | | | | |
|---|---|---|---|---|---|---|---|
| Clinical features[#] | Radiology[¶] | Histopathology[+] | Microscopy | Culture/PCR[§] | Aspergillus antibody | Aspergillus antigen[f] | Diagnosis |
| None | No change | ND | ND/- | + | - | ND/- | Colonisation |
| Yes >3 months | Cavities >3 months | ND/- | ND/- | + /- | + | ND/- | Consider CPA |
| Yes | New nodule <3 months | ND/- | ND/- | - | ND/- | ND/- | Possible IPA[##] |
| Yes | New cavity <3 months | ND/- | ND/- | - | ND/- | ND/- | Possible IPA[¶¶] |
| Yes | New <3 months | ND/- | ND/- | + | ND/- | ND/- | Probable IPA |
| Yes | New <3 months | ND/- | ND/- | - | + | ND/- | Probable IPA |
| Yes | New <3 months | ND/- | ND/- | - | ND/- | + ×2 | Probable IPA |
| Yes | New <3 months | ND/- | + | - | ND/- | ND/- | Probable IPA |
| Yes/no | Yes | + | ND/- | ND/- | ND/- | ND/- | Probable IPA |
| Yes/no | Yes | + | ND/- | + [§§] | ND/- | ND/- | Proven IPA |
| Yes/no | Yes | + | ND/- | ND/- | Any | + | Proven IPA |

The following points are noteworthy. 1) IPA may be upgraded when other diagnostic tests are available. 2) Treatment for proven and probable IPA are, first choice: voriconazole; second: caspofungin; and third: lipid formulation of Amphotericin B deoxycholate. 3) In the case of possible IPA, close follow-up and consider additional diagnostic procedures, such as imaging, flexible bronchoscopy, techniques to obtain histology if possible, should be caried out. ND: not done; CPA: chronic pulmonary aspergillosis [23]. +: positive; -: negative. [#]: Antibiotic-resistant exacerbation, pneumonia, pneumonitis or bronchospasm, typically in COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III or IV and currently or recently in receipt of corticosteroids. [¶]: Distinctive findings more obvious on thoracic computed tomography scan and include one or more cavities, new nodules or pleural-based lesions typical of pulmonary infarction. [+]: Dichotomous (45°) branching septate hyaline hyphae. [§]: PCR result can be accepted when licensed. [f]: Beware of false positives with some antibiotics, especially piperacillin/tazobactam. [##]: Consider alternative diagnosis, such as malignancy or other infections, e.g. cryptococcal or coccidioidal infection. [¶¶]: Consider alternative diagnosis such as mycobacterial or other fungal infections. [§§]: This result may be a standard culture or PCR result from another respiratory tract sample or from the biopsy or an immunology method of PCR specific to Aspergillus.

New drugs
Voriconazole
Efficacy of voriconazole (VRC) against IA was first demonstrated in some reports, including after the use of AmB-d, lipid formulation of amphotericin B deoxycholate, or itraconazole [32, 147–149]. These results were confirmed in a recent study that reported the superiority of VRC (two i.v. doses of 6 mg·kg$^{-1}$ on day 1 then 4 mg·kg$^{-1}$·12 h$^{-1}$ for ≥7 days, followed by 200 mg·12 h$^{-1}$ orally) versus AmB-d (i.v. 1–1.5 mg·kg$^{-1}$·day$^{-1}$) in a randomised, unblinded study that enrolled 277 patients. The survival rate at 12 weeks was 70.8 versus 57.9% (p=0.02) and drug-related events were observed in 343 versus 421 occasions (p=0.02) when VRC was compared with AmB-d [150].

| TABLE 6 | Treatment administered to patients in selected studies | | |
|---|---|---|---|
| Drugs used | Patients n | Outcome | Treatment[#] duration days |
| AmB-d | 24 | 22 D/2 S | 1–25/NA |
| AmB-d + inhaled AmB-d | 1 | S | 75 |
| AmB-d + instillation of AmB-d | 1 | D | NA |
| AmB-d + 5FC | 2 | 2 D | NA |
| AmB-d + ITZ | 6 | 6 D | 3–14 |
| AmB-d + ITZ + GM-CSF | 2 | 2 D | 17–23 |
| AmB-d followed by ABLC | 5 | 5 D | NA |
| ITZ followed by AmB-d | 1 | D | 6 |
| Fluconazole followed by AmB-d | 1 | D | 10 |
| No treatment | 13 | 13 D | |

Data from [12, 13, 34, 36, 37, 39–54]. AmB-d: Amphotericin B deoxycholate; D: death; S: survival; NA: not available; 5FC: 5-fluorocytosine; ITZ: itraconazole; GM-CSF: granulocyte-macrophage colony-stimulating factor; ABLC: amphotericin B lipid complex. [#]: Intravenous AmBd was administered at a daily dose of 0.1–1.3 mg·kg$^{-1}$ (data available in 25 patients) and ABLC at 5 mg·kg$^{-1}$·day$^{-1}$.

Although VRC appears to be well-tolerated, some clinical side-effects have been encountered frequently, such as visual disturbances (8–69%) and skin reactions (1–19%) [149–151]. Visual alterations included blurred vision, altered visual or colour perception, and photophobia. All these events were transient and resolved without intervention. Further human studies are needed to determine whether retinal changes observed in rats also occur during prolonged VRC therapy [151]. Among laboratory adverse events, increased liver function tests are encountered in 4.3–26.5% of patients, and the perturbation is more important with higher doses [149, 151–153]. Liver enzymes usually return to normal values after VRC discontinuation. Rare cases of hepatitis have been described [152, 154].

Due to accumulation of the VRC vehicle in the *i.v.* formulation when creatinine clearance is <50 mL·min$^{-1}$, oral administration is preferred as no adjustment in the dosage is necessary [151, 154]. Patients with moderate liver disease should receive a normal loading dose of VRC but the maintenance dose should be half the normal dose [151]. There are no safety data in patients with severe liver dysfunction. VRC is metabolised by the liver (CYP450 enzyme system) and is a substrate for and an inhibitor of the CYP2C9, CYP2C19 and CYP3A4 isoenzymes [149, 151]; thus, interaction problems can occur, as during itraconazole therapy (*e.g.* with phenytoin, rifampin, predniso-lone (increased area under curve of ~30%), warfarin, omeprazole, grapefruit juice, *etc.*; a more complete list is reported in recent papers [151, 152, 154]). The observation that hepatic toxicity might be dose related should prompt attention to the ''poor metaboliser'' population (the activity of the CYP2C19 is low in 20% of non-Indian Asians based on genetic features, and VRC blood levels can increase up to four times higher than in the ''normal metaboliser'' population) [154].

In addition, VRC can also be administered orally [151]. The absorption is better when administered either 1 h before or after a meal.

In summary, to date, voriconazole is the sole drug that has demonstrated a better efficacy than AmB-d. Moreover, the drug is available for *i.v.* and oral use. However, some concerns exist about drug interactions and adverse events. Caution should be exercised in case of renal failure (avoidance of *i.v.* preparation) and moderate liver dysfunction.

*Posaconazole*
Posaconazole is a new triazole that recently showed some efficacy for fungal prophylaxis in high-risk haematological patients. However, at present only the oral route is available and, to date, the drug is not recognised as a first-line therapy in IA [155–157].

*Echinocandin*
Echinocandin targets the synthesis of 1,3-β-D-glucan, a major component of the fungal cell wall [158]. The efficacy of a 70-mg first-day loading dose followed by 50 mg daily of caspofungin was assessed through a salvage study of 83 patients (mainly with haematological malignancy) with proven or probable IA (77% had IPA); a favourable response was demonstrated in 37 (44.6%) patients [159]. Importantly, tolerance to the drug is good, with only a few adverse events reported to date [159,

160], such as fever, phlebitis at the infusion site and some elevations in alanine aminotransferase, aspartate aminotrans-ferase and alkaline phosphatase levels (<5 times the upper limit of the normal range) [161].

No dosage adjustment is needed for patients aged >18 yrs, race, sex, renal impairment or haemodialysis, but a dose decrease to 35 mg·day$^{-1}$ after a full loading dose is suggested in case of moderate hepatic insufficiency [158, 161]. No data are available for severe liver disease. Caspofungin is not subject to drug interactions mediated by the cytochrome P450 system [158]. However, the co-administration with inducers of drug clearance and/or mixed inducer/inhibitor may result in reductions in caspofungin concentrations and, therefore, an increase to 70 mg·day$^{-1}$ may be necessary [158]. Capsfungin is available only as an *i.v.* preparation.

In short, echinocandin lipopeptides are a new class of antifungal agents that have demonstrated interesting activity against Aspergillus spp. Promising results have been reported in IPA. If these results are confirmed and are due to their excellent tolerance profile, these agents could be proposed as first-line therapy [162], like voriconazole. The main features of major antifungal agents are summarised in table 7.

Combination therapy
Although mortality rate is reduced by the use of VRC compared with AmB-d [150], outcome of patients suffering from IA remains uncertain. Therefore, with the introduction of the echinocandin class, which acts on another target in mould cell wall, it is possible that combination therapy can add some efficacy. The following beneficial effects could be expected: increased fungicidal activity; reduced side effects by diminishing doses of toxic drugs, such as AmB-d; and prevention of emergence of drug resistance. Laboratory data demonstrated additive-to-synergistic effects against *A. fumigatus* with the combination of caspofungin and AmB-d or itraconazole [158]. *In vitro* studies [163], some animal trials [164, 165] and few human reports suggest that the association of triazoles and echinocandin could improve the mortality rate in IA [166–171]. However, further clinical studies with combined therapy are needed before the concept can be validated.

Surgery
Although antifungal drugs represent the first choice in treatment of IA, eradication is rare as residual lesions are often present [159], and therefore potential recurrence is possible in the case of a new increase of immunodepression. To obviate IPA relapse, some authors have suggested the resection of residual lesion(s) in addition to medical therapy. This was suggested in patients suffering from haematological malignancies [18, 172–181]. In this setting, surgery was proposed when the lesions were close to pulmonary vessels to avoid life-threatening haemorrhage in the neutrophils' recovery period [18], or in case of diagnostic procedure. Nevertheless, surgical resection was associated with severe adverse events, including death, haemorrhage or pneumo-thorax [172, 174, 176, 181].

In COPD patients, surgical resection of IPA is generally excluded due to their poor pulmonary function, especially when corticosteroids are administered. Although surgery

| TABLE 7 | Main features of major antifungal agents | | | |
| --- | --- | --- | --- | --- |
| | **AmB-d** | **L-AmB** | **Voriconazole** | **Caspofungin** |
| **Administration route (dosage)** | *i.v.* (1–1.5 mg·kg$^{-1}$·day$^{-1}$) | *i.v.* (3–5 mg·kg$^{-1}$·day$^{-1}$) | *i.v.* (6 mg·kg$^{-1}$·12 h$^{-1}$[#] then 4 mg·kg$^{-1}$·12 h$^{-1}$) Oral (400 mg·12 h$^{-1}$[¶] then 200 mg·12 h$^{-1}$) | *i.v.* (70 mg[¶] then 50 mg·day$^{-1}$) |
| **Antifungal activity** | Reference drug | As AmB-d | More active than AmB-d | Salvage therapy |
| **Renal insufficiency** | Increased renal failure | No limitation | Oral route preferred if clearance <50 mL·min$^{-1}$ | No limitation |
| **Severe hepatic dysfunction** | No limitation | No limitation | Reduce the dose Monitor toxicity | Reduce the dose Monitor toxicity |
| **Major side effects** | Renal toxicity Electrolyte wasting Fever Poor clinical tolerance | As AmB-d but less frequently[+] | Visual disturbances Skin reactions Increased liver enzymes | Peripheral phlebitis Fever |
| **Drug interactions** | Few | Few | Numerous | Few |

AmB-d: Amphotericin B deoxycholate; L-AmB: lipid formulation of amphotericin B deoxycholate. [#]: Loading dose, for a total of two doses; [¶]: loading dose on day one; [+]: note that amphotericin B colloidal dispersion has more infusion-related toxicities than AmB-d.

could theoretically be considered in selected cases, both because it could be the only way to be fully curative and because minimal resection, such as wedge resection, might limit the functional defect [176, 180, 182], no recent study has been published to support this strategy.

Growth factors, cytokines and alternative therapies
*In vitro* studies found that corticosteroid-induced suppression of monocyte and neutrophils function was, at least partially, prevented by granulocyte-macrophage colony-stimulating factor (GM-CSF) and IFN-γ [58, 67, 183]. The beneficial effects of IFN-γ administration were also reported in patients suffering from chronic granulomatous disease [57, 184]. GM-CSF was added to IFN-γ for the treatment of a pseudomembranous necrotising bronchial aspergillosis. While the patient improved and survived, the relative contributions of antifungal agents and cytokines remain uncertain [185]. Clearly, more data are needed to assess the clinical usefulness of such drugs.

Some other therapeutic approaches have been reported, such as: the use of hyperbaric oxygenation for IA of the sinus [186]; the injection of AmB-d percutaneously in large pulmonary lesions from IA [187]; and the vaccination (either intranasally or subcutaneously) that could protect mice from lethal *A. fumigatus* infection [188]. However these approaches remain preliminary at this stage, the total number of patients included is still low and more studies are required to clarify their potential role in treatment of IPA. Other strategies using the immune pathways are under investigation and have been recently reviewed [62, 189].

**Prophylactic treatments**
Considering the poor prognosis of IPA and since early diagnosis and treatment improve the chance of survival, it is tempting to evaluate prophylactic treatment in patients at risk. However, data are lacking in COPD patients and results in haematological patients are not convincing.

**Prevention of infection**
As IPA diagnosis remains difficult and mortality rate is still high (up to 90%, depending on the underlying disease), prevention of infection is very important [9]. As a consequence, inside the hospital, it seems reasonable to eliminate obvious environmental sources of Aspergillus spp. and also by cleaning all the surfaces to avoid dust accumulation. In addition, to prevent outbreaks, environmental protection by elevating impenetrable barriers must be implemented during construction [190]. As has been proven for haematological patients [191], COPD patients should be advised to wear a high-efficiency mask, or to avoid exposure, whenever the risk of inhaling a large amount of Aspergillus during a transient environmental exposure is high. Due to permanent exposure to risk factors (*e.g.* corticosteroids) and their huge cost, high-efficiency particulate air filtration and laminar flow rooms are not applicable *per se* for COPD patients, although some effectiveness has been demonstrated for haematological patients [192].

Outside the hospital, while specific methods to control or eliminate Aspergillus spp. from the environment are lacking, prevention must be focused on the avoidance of high load sources, *e.g.* constructions, cellars or lofts, composts, *etc.* Recent reports suggest that IA could also be a water-acquired infection [193] and that pillows may contain high loads of Aspergillus [194]. Finally, if the patient is receiving corticosteroids, the dose should be decreased as much as is possible or even stopped altogether.

**PROGNOSIS**
Despite treatment, the IPA mortality rate remains high. In their review of the literature, LIN *et al.* [24] report an overall mortality of 58%, but reaching 86.7% for bone marrow transplant recipients and 88.1% for patients with central nervous system or disseminated aspergillosis. In another study, a favourable response (both complete and partial) to

| TABLE 8 | Future research needed to better identify Aspergillus infection in chronic obstructive disease (COPD) patients and to decrease mortality from the disease |
|---|---|

**Epidemiology**

1) Incidence of IPA *versus* Aspergillus colonisation in COPD population

2) Role of steroids (dose?; inhaled?) in predisposing to IPA

3) Existence of specific risk factors related to COPD patients

**Diagnosis**

1) Validation of diagnostic algorithms

2) Place of noninvasive tests including antigenaemia,

Aspergillus antibody detection and molecular diagnosis

**Treatment**

1) Validation of voriconazole as first-line therapy

2) Place of combination therapy

3) Place of surgery

4) Immunotherapy

**Prevention**

1) Are there some reliable measures to protect COPD population?

IPA: invasive pulmonary aspergillosis.

treatment was reported in 56% of patients with pulmonary diseases (no other specification was given) [25].

In contrast, when COPD criteria were clearly mentioned, all but three patients reported in the literature died despite treatment administration in 77% (table 6), and intensive care unit admission did not seem to modify this poor prognosis [12, 15, 16]. The duration between symptoms and diagnosis (table 2) may, at least partially, explain this very high mortality.

## CONCLUSIONS

Although Aspergillus colonisation is frequent in COPD patients, IPA can occur and prompt diagnosis is important to provide the maximum chance of successful treatment. The first clinical signs are often protracted bronchospam and/or antibiotic-resistant lower respiratory tract infection. In this context, the presence of Aspergillus spp. in the sputum must be regarded as the first clue of infection. As the chest radiograph may be normal early on in the course of the disease, a prompt CT scan is required to visualise mild alterations of the lung parenchyma. When possible, bronchoscopy is required to demonstrate mucosal modifications and allow biopsies, as well as BAL. There are insufficient data to support the use of serological tests. If the patient's status is severe, prompt therapy should be implemented to give the patient optimal chance of cure and, thereafter, diagnostic procedures must be conducted to confirm the clinical suspicion of IPA. Although AmB-d has been most extensively studied, the results of more recent studies suggest that VRC should be the first choice therapy. Patients receiving chronic steroid therapy should be provided with information on how to prevent contact with environmental sources of Aspergillus spp.

Clearly, more work needs to be carried out in order to better identify Aspergillus infection in chronic obstructive pulmonary disease patients and to decrease mortality from this devastating disease. Table 8 illustrates some of the important issues that require further clarification.

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