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Invasive pulmonary aspergillosis in critically ill immunocompetent patients

Aspergillose pulmonaire invasive chez le patient immunocompétent en réanimation

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Abstract Invasive pulmonary aspergillosis (IPA) is a severe and well recognized infection in patients with hematological malignancies. However, increasing number of studies has reported the emergence of IPA in critically ill immunocompetent patients, mainly represented by chronic obstructive pulmonary disease (COPD) patients, with an estimated incidence of 2%. These patients are characterized by multifactorial impairments in their local defense. The major risk factors are systemic steroid use and administration of broad-spectrum antibiotics. IPA is responsible for high mortality, and its usual clinical, radiological, and biological specificities are generally absent in the immunocompetent patient. Rapid diagnosis requires histological evidence. Sensitivity of lower respiratory tract cultures and serology remains poor. The detection of galactomannan fungal antigen in the bronchoalveolar lavage may offer an interesting alternative diagnostic tool. The first-line recommended antifungal treatment is voriconazole, but other therapies exist like amphotericin, which was largely used in the past. We conducted a literature review focusing at IPA in the critically ill immunocompetent patients, in order to analyze its epidemiology, physiopathology, prognosis, diagnostic methods, and treatment.

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Résumé L'aspergillose pulmonaire invasive (API) est une infection sévère dont la prise en charge est bien codifiée chez les patients présentant des hémopathies malignes. Un nombre croissant d'études rapporte l'émergence d'API dans les populations non immunodéprimées en réanimation, représentées principalement par les patients atteints de bronchopneumopathies chroniques obstructives (BPCO), avec une incidence estimée à 2 %. Cette catégorie de patients présente une altération multifactorielle de leurs défenses locales, et les facteurs de risque les plus importants sont l'utilisation de corticoïdes systémiques et l'administration d'antibiotiques à large spectre. L'API est responsable d'une mortalité importante, et ses caractéristiques spécifiques clinicoradiologiques et biologiques sont généralement absentes dans ce contexte. Par conséquent, une meilleure compréhension de sa pathogenèse et une connaissance approfondie de ses spécificités en réanimation sont nécessaires pour permettre un diagnostic plus précoce. L'obtention d'une preuve histopathologique certifie le diagnostic. La sensibilité des cultures des prélèvements respiratoires ainsi que des sérologies est faible. La détection de l'antigène fongique galactomannane dans le lavage bronchoalvéolaire semble être de valeur diagnostique intéressante. Le traitement antifongique recommandé en première intention est le voriconazole, mais il existe des alternatives largement utilisées dans le passé comme l'amphotéricine B. Nous avons conduit une revue de la littérature étudiant l'API chez les patients non immunodéprimés en réanimation, afin d'analyser les données concernant l'épidémiologie, la physiopathologie, le pronostic, les méthodes diagnostiques et les options thérapeutiques.

Mots clés *Aspergillus* · Aspergillose pulmonaire invasive · BPCO · Galactomannane · Unité de soins intensifs

Introduction

Aspergillus species are ubiquitous fungi, responsible for a large spectrum of infectious diseases like tracheobronchitis, chronic necrotizing pulmonary aspergillosis, mycetoma, and invasive pulmonary aspergillosis (IPA), as well as immunological manifestations like chronic broncho-pulmonary allergic aspergillosis. There are over 200 types of *Aspergillus*, although *A. fumigatus* is the most common species found in humans [1]. The main route to infection is inhalation of airborne conidia dispersed in the air, followed by their deposition in the respiratory tract and alveolar space. Its pathogenesis is regulated by a multifactorial alteration of host defenses, including local and systemic immune deficiency, mechanical mucociliary impairment, and co-bacterial colonization. IPA is a life-threatening pneumonia characterized by parenchymal lung invasion and vascular erosion, and it has been extensively studied in immunocompromised patients, especially those with hematological malignancies and hematopoietic stem cell transplants, with well-established diagnostic criteria. The European Organization for the Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) has defined three categories for IPA: proven, probable, and possible, according to a combination of host factors, clinical features, and microbiological results [2]. However, numerous series of IPA occurring in critically ill non-neutropenic individuals are increasingly reported, and other categories of population at risk are being identified, dominated by chronic pulmonary diseases such as chronic obstructive pulmonary disease (COPD) [3–6]. The high mortality found in these patients, along with the difficulties encountered to make an early diagnosis, incites intensive care physicians to have broader clinical, biological, and radiological considerations when IPA is suspected.

This article focuses on identifying the critical points that make the diagnosis of IPA in immunocompetent patients admitted to intensive care units (ICUs) a challenge. It aims at reviewing epidemiological characteristics, risk factors, pathophysiological mechanisms, and diagnostic tools relevant to the diagnosis of IPA and factors that lead to the decision to implement antifungal treatment in the ICU setting.

Epidemiology

Incidence

Proven IPA requires histopathological proof showing angular dichotomously branching septate hyphae on microscopic examination [2]. This is not too often possible in critically ill patients because of several contra-indications, and because *post-mortem* diagnosis by autopsy is rarely performed. Hence, an accurate estimation of incident cases of IPA in the ICU is difficult. In 2003, Dimopoulos et al. found, in an autopsy study of 222 ICU patients, 6 (2.8%) patients with disseminated aspergillosis including 5 (2.3%) with COPD [7]. Another approach consists in taking all fatal cases of IPA in the ICU and searching for associated comorbidities. In a meta-analysis of 53 studies, done by Lin et al., from 1995 to 1999 including 1941 patients with proven or probable IPA, 388 (20%) had an underlying pulmonary disease, including 26 (1.6%) with COPD [3]. A retrospective study done by Meersseman et al., between 2000 and 2003 in 1850 ICU patients, found 89 (4.8%) cases of IPA without hematological malignancy, including 35 (1.8%) with COPD [8]. A multicenter prospective study conducted over a 9-month period in 73 ICUs found *Aspergillus* spp. isolates in 36 (2%) out of 1,756 patients [5]. Among this group, 20 (1.1%) were interpreted as having IPA. Another retrospective study using a historical cohort of 25,216 critically ill patients found 172 (0.6%) with a positive respiratory tract culture for *Aspergillus*, including 83 (0.33%) classified as IPA [9]; 50 (60%) of these patients had no high-risk predisposing hematological conditions. Detection of *Aspergillus* in endotracheal aspirate cultures is observed in up to 2% of mechanically ventilated ICU patients [5,9,10]. However, the distinction between the acquisition of IPA in the ICU setting and the community setting is scarcely clarified in the mentioned studies. This is the reason why a precise evaluation of the hospital- or ventilator-acquired IPA incidence is difficult.

Risk factors

COPD

As seen above, COPD patients represent the main group at risk in populations without hematological malignancy. Advanced COPD stages III and IV are correlated with a higher risk of IPA. In the series of 53 patients with probable IPA, 32 (60.3%) patients had stage III disease and 21 (39.7%) had stage IV disease according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [4]. However, another retrospective case-control study comparing 60 COPD patients with IPA versus 30 COPD patients without IPA showed no statistical difference in the distribution of stage III or IV disease in the two sub-groups [6]. Moreover, five patients with IPA had stage II disease. Besides chronic respiratory diseases, on a lesser but non-negligible scale, other host factors are reported as risk factor such as solid organ transplants [11], liver cirrhosis [11], and chronic systemic disease requiring immunosuppressive therapy on the long term [11].

Corticosteroids

Corticosteroid use before admission is a risk factor in series reporting IPA in COPD patients [4,12,13]. A previously

mentioned study found that the accumulated doses of corticosteroids (>700 mg of prednisone) received during the 3 months prior to admission significantly increased the risk of IPA occurrence in COPD patients [4]. Other studies have suggested that cumulative doses of corticosteroids exceeding 350 mg (prednisone dose) were highly related with IPA occurrence in COPD patients [12,13]. Some reports have even evoked a plausible role of inhaled steroids in the emergence of IPA in COPD patients [14–16].

Broad-spectrum antibiotics

The use of broad-spectrum antibiotics to treat acute bacterial exacerbation within 3 months before admission, and the prescription of three or more broad-spectrum antibiotics in hospital are factors that were found to be significant predictors of IPA in patients with COPD [4,13]. These risk factors have led to the proposal made by Bulpa et al. in 2007, of an adapted version of IPA diagnostic criteria, to standardize definitions in the non-immunocompromised population, focusing on COPD patients [17]. In this version, proven IPA still requires histopathological or cytopathological examination. Probable and possible IPA involve severe COPD patients (stage III or IV according to the GOLD classification), usually treated with steroids, with a history of recent episode(s) of dyspnea exacerbation and compatible radiological lesions, combined or not with positive microbiological findings.

Liver disease

Occurrence of IPA has been reported in patients with severe liver disease such as end-stage cirrhosis and acute hepatic failure, even in patients free of immunosuppressive treatments [18,19]. This is partially explained by the decreasing peripheral CD3 and CD4 T-lymphocyte count in severe cirrhosis [20], exposing these patients to opportunistic fungal infections.

Mortality

IPA mortality in COPD and critically ill patients is very high and ranges from 67% to 100%, even when adequate antifungal therapy is given, explaining why IPA is generally presented as a "terminal" fungal disease [5,7,11,21–24]. Its related mortality is generally superior to those predicted by the usual scoring systems (APACHE II, SAPS II) [11]. These results can be partially explained by the delay in diagnosis, and initiation of appropriate treatment. In contrast, it is interesting to notice an inverted trend in recipients of hematopoietic stem cell transplants, among whom IPA-attributable mortality has significantly decreased over the years from 70% to nearly 40% [25].

Pathophysiology

Taking the example of COPD patients, invasion of the lung by *Aspergillus* is a complex multifactorial process. Several mechanisms are involved, which clearly differ from neutropenic patients with hematological disorders. Taken together, these factors lead to a "pseudo-immunocompetent" state, which predisposes patients colonized with filamentous fungi to invasive parenchymal disease.

Changes in lung function and morphology over time

Chronic airway inflammation alters the mechanical clearance of inhaled conidia by the mucociliary system [26]. Tracheal and sinusal explant models have shown that *A. fumigatus* culture filtrates inhibit ex vivo ciliary beat frequency, probably due to metabolites like gliotoxin and verruculogen [27,28]. Moreover, parenchymal distortion and structural remodeling like bronchiectasis may create chronic trapped *Aspergillus* niches [29]. High-resolution CT scans show that bronchiectasis is common in advanced COPD, creating pockets of chronic, low-grade, local infection [29]. The importance of *Aspergillus* inoculum on survival has been experimentally studied in murine models, and was associated with a higher mortality [30–32]. In individuals without hematological immunodeficiency, the inoculum required to initiate invasion is likely to be large, although no human study allows us to confirm this fact.

Impaired lung defenses

Impairment of immune host defenses plays a major role in IPA pathogenesis. Airway macrophages ingest and destroy conidia; germinating spores and hyphae are attacked by polymorphonuclear neutrophils (PMNs) [33]. COPD is a chronic inflammatory disease characterized by increased recruitment and activation of eosinophils, pulmonary alveolar macrophages (PAMs), and lymphocytes within the lungs, but their immune function of phagocytosis and chemotaxis is qualitatively altered [34,35]. Evidence now shows that the disease progresses to systemic autoimmunity, possibly through spillover from the primary pulmonary inflammatory input [36–38]. The recognition of pathogen-associated molecular patterns by host cell pattern recognition receptors (PRRs) is the first step of phagocytosis, leading to a proinflammatory response characterized by the production of cytokines and chemokines including tumor necrosing factor (TNF-α), interleukin (IL)-1, IL-6, IL-8, and many others, necessary for host defense. Toll-like receptors (TLR) 2 and TLR 4 are among the most recognized PPRs, and a decrease in their expression in COPD patients might diminish the initial innate immune response against *Aspergillus* [39,40]. Corticosteroids contribute as well to the development of

IPA by inhibiting the phagocytosis functions of PAMs and PMNs [41,42], and might even stimulate the growth of *A. fumigatus* via a sterol-binding protein, as suggested by one in vitro study [43].

Bacterial co-infection and chronic colonization

COPD patients present frequent bacterial exacerbations, leading to broad-spectrum antibiotics, which could bolster fungal emergence in the airways. *Pseudomonas aeruginosa*, a Gram-negative non-fermenting bacteria, mostly found in severely advanced diseases and patients with worse pulmonary function often requiring mechanical ventilation, is known for its great mutational and biofilm-producing abilities, conferring it increased antibiotic resistance [44]. Since *A. fumigatus* has been shown to grow as a biofilm in vivo, the possibility of an interaction between these two species has been evoked, with *P. aeruginosa* providing biofilm niches allowing the expansion of fungal colonies [45].

Nutritional status

Association between weight depletion and mortality has been demonstrated in patients with COPD [46]. Nutritional status may influence the occurrence of acute exacerbations, major promoter of the development of severe lung infections requiring ICU.

Assessing the diagnosis of IPA

The factors potentially involved in the pathogenesis of IPA in non-neutropenic ICU patients with chronic lung diseases clearly indicate that the IPA diagnosis is difficult. Early identification of patients who require antifungal treatment, especially among mechanically ventilated patients, relies on the ability of trained physicians to discriminate acute infection rather than chronic colonization.

Radiological findings

Chest CT scans are an important tool for the diagnosis of IPA in neutropenic patients, but not for non-neutropenic patients. In immunocompetent patients, chest CT scans rarely find the pathognomonic halo and air crescent signs, with poor sensitivity ranging from 5 to 24% [9,11,47,48]. Instead, a wide spectrum of abnormalities are described, including progressive infiltrates, nodules, consolidations, cavitations, diffuse reticular or alveolar opacities, and pleural fluid [6,17]. These findings remain nonspecific and are frequently found in an ICU setting, especially in mechanically ventilated patients, where a differential diagnosis with cardio-respiratory failure or a bacterial infection remains difficult. However, several reports suggest that persistent or rapidly progressive abnormalities on thoracic imaging, despite broad-spectrum antibiotics in patients with COPD, should be considered as marker for IPA, especially when combined with clinical isolation of *Aspergillus* filaments. Guinea et al. illustrate clearly this aspect in their study, in which worsening of radiological data was observed in 66% of the 53 COPD patients with IPA, as compared with 6.4% of the COPD patients without IPA [4].

Histopathology and clinical algorithm

As previously mentioned, the presence in a lung fragment of angular, dichotomously branching septate hyphae on direct microscopic examination of lung specimen obtained by biopsy or needle aspiration assesses the diagnosis of IPA. Open lung biopsy in ICU patients is rarely feasible. For example, none of the 53 COPD patients included in the large series of IPA published by Guinea et al. had lung biopsy [4]. For that reason, most cases of IPA reported in non-neutropenic ICU patients are categorized as "probable" using EORTC criteria. A recently published observational multicenter study was conceived by Blot et al. to validate a new clinical algorithm to discriminate *Aspergillus* colonization from putative IPA, in critically-ill patients with one or more *Aspergillus*-positive endotracheal aspirates [10]. The study included 524 patients, including 115 histopathology-controlled patients. Seventy-nine patients among these 115 had proven aspergillosis. COPD was the most represented underlying disease (26% of the patients). Using the EORTC/MSG criteria, 32 (6.1%) patients had probable aspergillosis and 413 (78.8%) patients were not classifiable, whereas the algorithm judged 199 (38%) patients to have putative aspergillosis and 246 (47%) to have *Aspergillus* colonization. Among the 115 histopathology-controlled cases, the algorithm judged 86 (74.7%) to have putative aspergillosis; this diagnosis was confirmed in 72 of them, resulting in 14 false positives. The algorithm suggested *Aspergillus* colonization in 29/115 (25.5%) cases; this was confirmed in 22 of them, resulting in 7 false negatives. The clinical algorithm had a specificity of 61% and a sensitivity of 92%. In all the patients with histopathological proof, while assuming IPA prevalence of 40%, the algorithm had a positive predictive value and a negative predictive value of 61 and 92%, respectively. Putative IPA had a similar mortality (70%) to probable (72%) and proven (78%) IPA. One of the inconveniences of this algorithm is the requirement of an *Aspergillus*-positive culture, which excludes, as seen earlier, a considerable proportion of patients due to its low sensitivity (12 to 67%). However, this is the first article to date that validates such an algorithm, with a satisfying sensitivity, in comparison to the gold-standard with an extensive series of

histopathology-controlled cases [10]. In the light of the available literature data, its use should be integrated in our clinical daily practice.

Biologic findings

Culture based-methods

The isolation of *Aspergillus* in sputum and upper respiratory tract samples remains of unknown clinical significance in patients at risk for ICU admission such as COPD patients presenting symptoms of infectious pneumonia. A prospective multicenter survey of *Aspergillus* in 11,368 respiratory tract samples found 151 (1.33%) positive cultures, out of which 88% were considered as colonization, 7% had probable IPA, and 2% had proven IPA [49]. Fiberoptic bronchoscopy may provide a wider exploration of the lower respiratory tract through endotracheal aspirate and broncho-alveolar lavage, and it is routinely feasible in ICU mechanically ventilated patients. The clinico-pathological pattern of IPA is likely to affect the positivity of broncho-alveolar lavage (BAL) cultures, with higher results found in the airway-invasive form than in the angioinvasive form [50]. In immunocompromised high-risk patients, positive culture results were associated with IPA in 50 to 60% of cases [2]. In non-hematological patients, sensitivity is even lower and ranges from 12 to 67% [5,9,13]. Quantitative data could be interesting, since a case-definition study in immunocompromised patients showed that cases with proven IPA had a significantly higher number of *Aspergillus* colonies [51]. Overall, positive respiratory cultures for *Aspergillus* filaments should not be neglected and should raise the suspicion of IPA, especially in COPD patients cases associated with steroid use and antibiotic-resistant pneumonia. Additionally, repeatedly positive cultures with the same mould strain are even more suggestive of invasive infection, and whenever it is possible, lower tract samples should be preferred.

Serology

A serum antibody test for *A. fumigatus* figures as one of the biologic criteria proposed by Bulpa et al. for the diagnosis of IPA in COPD patients and is suggested by other authors [17,52]. However, in patients treated with corticosteroids, weaker immune antibody response is mounted, leading to decreased sensitivity of serology results. Another factor is the rapid course of IPA, which limits the initiation of an explicit humoral response. Nevertheless, monitoring of antibody titers is likely to be useful for detecting the transition from chronic semi-invasive disease to IPA [53]. A comparative study over a 6-year period between 88 neutropenic and non-neutropenic patients with IPA diagnosis, 37 patients (42%) had at least one antibody test, which was positive in 30% of cases [54]. In non-neutropenic patients, the sensitivity of antibody testing was 48%, whereas only 6% in patients with severe neutropenia [54].

Antigen detection

• Galactomannan

Galactomannan (GM) is a polysaccharide cell-wall component that is released by *Aspergillus* during hyphal growth, which constitutes an exoantigen marker for IPA diagnosis. A meta-analysis of serum GM assay in immunocompromised patients showed had a sensitivity of 71% and a specificity of 89% for proven cases of IPA, with values above 90% in prolonged neutropenia and hematopoietic stem cell recipients [55]. For non-neutropenic patients, including COPD, sensitivity for the serum GM assay is lower due to the role played by PMNs in the clearance of GM from the blood before it can be detected. In a retrospective study of IPA in patients without malignancy admitted to a medical ICU, sensitivity of GM assay in serum was 53% [11]. In Guinea's large retrospective series of IPA in COPD patients, 33/53 (62%) with probable IPA were tested for serum GM, and the result was positive in 14 (42.4%), using a cut-off value of 0.5 ng/ml [4]. Besides its low sensitivity ranging from 4 to 55%, another drawback of GM testing is the well-known risk of false-positive results in patients treated with piperacillin-tazobactam [56–62]. Several studies evaluated this risk in patients treated with different batches of this antibiotic and found false-positive results in nearly 70 to 86% of the cases. However, in a recent study where serum samples were obtained from HSCT recipients, 25 (1.6%) of 1606 samples tested positive for GM in the absence of antibiotics versus 10 (2.5%) of 394 samples drawn while on piperacillin-tazobactam [58]. This difference was not statistically significant, suggesting that currently available preparations seem no longer responsible for false-positive results. Other false-positive results are represented by the translocation through the gastro-intestinal tract of fungal GM from contaminated food with high carbohydrate content, and the use of parenteral nutrition and amoxicillin-clavulanate [61,63]. On the other hand, sensitivity of GM assays may be decreased in patients receiving concomitant antifungal therapy [64,65]. GM can also be usefully detected in BAL fluid, and its sensitivity using ELISA methods in patients with hematological malignancies and solid organs transplant recipients ranges from 85 to 100% [63,66–69]. In a prospective study conducted in 110 ICU patients, there were 26 proven IPA cases, and the sensitivity of GM detection in BAL fluid was 88%, with a specificity of 87% (cut-off value of 0.5 ng/mL) [70]. Median indices were nearly 4 and 1.5 for patients with proven and probable IPA, respectively.

Interestingly, in 11 of the 26 proven cases, BAL culture and serum GM remained negative, whereas GM in BAL fluid was positive [70]. In a recent multicenter prospective study including 47 COPD patients receiving corticosteroids who demonstrated a new lung infiltrate while on mechanical ventilation in the ICU, GM levels in respiratory samples (blind tracheal washings) were >0.5 ng/mL in 74.5% of patients, >1 ng/mL in 40.5% of patients, and >1.5 ng/mL in 21.3% of patients [71]. No cut-off value was suggested to distinguish IPA from colonization, and no specific factor was associated with false-positive results.

Understanding the invasion of the alveolar-capillary membrane by hyphae can help explain the differences between serum and BAL GM levels. Hope et al. elegantly demonstrated in an in vitro bilayer model of the human alveolus that the alveolar-capillary barrier is breeched approximately 14 to 16 hours post-inoculation, which coincided with the beginning of the increase in GM serum levels [72]. Time-courses of GM concentrations in the endothelial and alveolar compartments are discordant, suggesting that GM does not intrinsically cross the alveolar-capillary barrier and that its presence in the bloodstream corresponds to the physical presence of hyphae.

• 1-3-β-D-glucan

1-3-β-D-glucan is the cell-wall polysaccharide of most fungi including *Aspergillus* and *Candida*. Detection of its antigen has been proposed as a diagnostic tool for IPA, but the test lacks specificity, and it is commonly detected in ICU patients without any evidence of invasive fungal infection [73,74]. Therefore, the use of 1-3-β-D-glucan in IPA diagnosis is not recommended and needs further investigation.

The summary of the IPA definition criteria is presented in Table 1.

Treatment

The mainstay of IPA treatment is represented by two antifungal agents, voriconazole and amphotericin B, recommended as first-line therapy. Other drugs like itraconazole, caspofungin, and posaconazole have been evaluated, mainly in hematological patients. However, to date, they are not recognized as first-line therapy, but only as alternative treatment in refractory IPA.

Table 1 Summary of the IPA definition criteria as proposed by the European Organisation for Research and Treatment of Cancer EORTC (EORTC) [2], Bulpa [17], and Blot [10]

Criteria	Histopathology	Host factors	Clinical signs	Radiological signs	Culture	Serum antibody test	Serum GM antigen	BAL GM antigen
EORTC								
Proven	+							
Probable		+[1]		+[2]	+[3]	+	+	+
Possible		+		+	–	–	–	
Bulpa								
Proven	+				+[4]	+	+	
Probable	+	+[5]	+	+	–	–	–	
					+	+	+	
Possible		+	+	+	–	–	–	
Colonization		+	–	–	+			
Blot								
Proven	+							
Putative		+[1]	+[6]	+	+[7]			
Colonization		+	+	+	+			

GM: galactomannan, BAL: broncho-alveolar lavage.

[1] Neutropenia <500/mm³, hematopoietic stem cell transplant, use of corticosteroids, T-cell immunosuppressants, inherited severe immunodeficiency; [2] Dense well-circumscribed lesions with or without halo sign, air crescent sign, cavity; [3] Sputum, BAL, or bronchial brush indicating the presence of fungal elements or *Aspergillus* spp.; [4] Lower respiratory tract sample; [5] Chronic obstructive pulmonary disease (COPD) patients, usually treated with steroids, and severe (GOLD stage III or IV); [6] Refractory or recrudescent fever despite antibiotic therapy, pleuritic chest pain, pleuritic rub, dyspnea, hemoptysis, worsening respiratory insufficiency despite antibiotics and ventilatory support; [7] BAL fluid.

Voriconazole

In 2002, a randomized, unblinded trial compared a triazole drug, voriconazole, in 144 patients *vs* amphotericin B deoxycholate in 133 patients for primary treatment of IPA, mostly in neutropenic hematological patients [75]. Voriconazole was associated with better responses and significantly higher survival rate at 12 weeks (70.8%) compared to the amphotericin B group (57.9%). Severe side effects were significantly lower in the voriconazole group, although 44.8% of them had transient visual disturbances (blurred vision, altered visual or color perception, and photophobia). One biological adverse effect was the increased liver enzymes in 4.3 to 26.5% of patients, although rare cases of hepatitis were described. However, the study included a majority of patients with hematological malignancies, and only 5.7% of them were receiving corticosteroids as a predisposing condition. Lortholary et al. conducted a multicenter surveillance study in 12 French university hospitals including 393 patients with probable or proven IA, out of which 9 had chronic pulmonary diseases (2.3%) [76]. The 12-week overall mortality was significantly lower (40%) when first-line therapy included voriconazole alone or in combination, compared to other regimens excluding voriconazole (60%) [76]. However, in the particular subset of COPD patients, the superiority of voriconazole over lipid formulations of amphotericin B or echinocandins has not been definitely proved. Voriconazole could be administered intravenously (IV) or orally, and caution should be made when it is used because of drug interactions. The IV dose regimen consists of a loading dose of 6 mg/kg/12 h during 24 hours, followed by 4 mg/kg/12 h. The oral dose regimen consists in a loading dose of 400 mg/12 h during 24 hours, then 200 mg/12h.

Amphotericin B

Amphotericin B deoxycholate, a natural polyene macrolide antibiotic, has been the standard therapy for IPA for a long time because of its broad antifungal activity and low cost. Amphotericin B administration is frequently associated with infusion-related side effects (fever, hypotension, chills) and nephrotoxocity, which is dose-dependent. This has led to the use of amphotericin B lipid formulations because of their better clinical and biological tolerance. Usual doses range from 1 to 1.5 mg/kg/day IV for amphotericin B desoxycholate, and from 3 to 5 mg/kg/day IV for its lipid formulations.

Itraconazole

Itraconazole is another triazole drug suggested for IPA treatment. In a prospective, open, and multicenter trial, the efficacy and safety of itraconazole IV followed by the oral form were evaluated [77]. A complete or partial response was observed in 15 (48%) patients out of 31. Another multicenter, open study including 76 patients with IPA found 30 patients (39%) with complete or partial response [78].

Posaconazole

Posaconazole is a recent triazole that recently showed efficacy for fungal prophylaxis in high-risk hematological patients [79,80]. Only the oral formulation has been studied and the dose regimen for prophylaxis is 200 mg 3 times per day, and 800 mg for salvage treatment, administered in 2 or 4 divided doses [81].

Caspofungin

Caspofungin belongs to the echinocandins class, targeting the synthesis of 1-3-β-D-glucan. A salvage study of 83 patients (mainly with hematological malignancies) diagnosed with proven or probable IPA showed a significant clinical response 37 (44.6%) patients, with a good tolerance profile [82,83]. The dose regimen consists in 70 mg first day IV loading dose followed by 50 mg/day IV.

Combination therapy

Additive and synergistic effects against *A. fumigatus* are noted when a combination of caspofungin and Amphotericin B or itraconazole is used. Other in vitro studies and animal trials [17,84,85], along with several reports in immunocompromised patients suggest that a combination therapy could provide beneficial effects on IPA mortality [17,76,86,87].

Optimal duration of therapy for IPA is yet to be defined. Treatment is generally continued until resolution or stabilization of clinical and radiological symptoms occur.

Surgery

Surgery has been mostly evaluated in limited series of patients with hematological malignancies, as a complementary treatment when axial mediastinal blood vessels were at risk of invasion and thus for cataclysmic hemorrhage. However, surgery was often associated with a 30-day mortality ranging from 6 to 54% [88–90]. On the other hand, in COPD patients, no published data allows the recommendation of this type of treatment, especially in a subgroup that already suffers from poor pulmonary function.

Prophylaxis

Regarding the use of antifungal prophylaxis in a selected subset of patients at risk for IPA such as COPD patients, no convincing data exists so far to adopt such strategies.

Conclusion

IPA is a severe fungal disease that affects 1.3 to 2.3% of COPD patients admitted to the ICU. It remains underestimated in this subset of patients because of the lack of specific clinical and radiological criteria that are usually found in hematological populations. Despite the arrival of a new generation of effective and well-tolerated antifungal agents, prognosis remains poor and the mortality is very high. The host factors that contribute to the development of IPA include impairment of the innate lung defenses, steroid-induced immunomodulation, and chronic bacterial colonization status responsible for acute exacerbations and subsequent fungal colonization. A better understanding of its pathogenesis and thorough investigation of risk factors are the key steps to identify patients at high risk admitted to the ICU, such as advanced COPD disease (stages III and IV GOLD), recurrent or recent use of steroids, and use of broad-spectrum antibiotic for the treatment of a resistant pneumonia. Clinical and radiological signs are non-specific, and persistent or rapid developing infiltrative abnormalities despite broad-spectrum antibiotics are strongly in favor of IPA. The recovery of positive *Aspergillus* culture samples must not be disregarded, and should lead to further investigations, in order to initiate appropriate antifungal therapy. The low sensitivity of serum GM and respiratory tract cultures in COPD patients is a major setback, but detection of GM in BAL fluid seems to be the most promising diagnostic tool for ICU practitioners. The same set of treatment recommendations applies for the treatment of IPA in COPD than for neutropenic patients, although more prospective and comparative studies are needed to validate the current algorithm in order to improve the diagnosis and the outcome of IPA in the critically ill patients.

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