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REVIEW

Management of invasive aspergillosis in patients with COPD: Rational use of voriconazole

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Abstract: Invasive pulmonary aspergillosis (IPA) is an important cause of mortality in patients with hematologic malignancies. The reported incidence of IPA in the context of chronic obstructive pulmonary disease (COPD) seems to increase. Approximately 1%–2% of overall fatal cases of IPA occur in COPD patients. The combination of factors such as lung immune imbalance, long-term corticosteroid use, increasing rate of bacterial exacerbations over time, and malnutrition are responsible for the emergence of IPA in these patients. The diagnosis of IPA is difficult to establish, which explains the delay in implementing accurate antifungal therapy and the high mortality rate. Persistent pneumonia nonresponsive to appropriate antibiotic treatment raises the concern of an invasive fungal infection. Definite diagnosis is obtained from tissue biopsy evidencing *Aspergillus* spp. on microscopic examination or in culture. Culture and microscopy of respiratory tract samples have a sensitivity and specificity of around 50%. Other diagnostic tools can be useful in documenting IPA: computed tomography (CT) scan, nonculture-based tests in serum and/or in bronchoalveolar lavage such as antibody/antigen tests for *Aspergillus* spp. More recent tools such as polymerase chain reaction or [1→3]-β-D-glucan have predictive values that need to be further investigated in COPD patients. Antifungal monotherapy using azole voriconazole is recommended as a first-line treatment of IPA. This review assesses the use of voriconazole in COPD patients.

Keywords: chronic obstructive pulmonary disease, corticosteroid, *Aspergillus*, invasive pulmonary aspergillosis, voriconazole

Introduction

Invasive pulmonary aspergillosis (IPA) is a life-threatening pneumonia characterized by lung parenchyma invasion with vasculature erosion and necrosis that is caused by opportunistic fungi belonging to the species *Aspergillus*. *Aspergillus fumigatus* is the most common species recovered from cases of IPA.[1] The major risk factor for IPA development is host immunosuppression, especially related to long-term systemic phagocytic depletion. Consequently, IPA has been strongly associated with hematological cancer patients (including recipients of hematopoietic stem cell transplants) despite efforts over the past two decades to reduce its incidence, and improve diagnosis and treatment methods.[2] Other subsets of high-risk patients include solid-organ transplant recipients, patients with advanced HIV infection, inherited immunodeficiency, those receiving other immunosupresors such as monoclonal antibodies, and critically-ill patients. Of particular concern are patients who may not be obviously immunocompromised but combine lung immune imbalance with a systemic intrinsic and/or corticosteroid-induced immune dysfunction.

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These patients do not strictly match with hematological cancer patient criteria regarding clinical presentation, radiological findings, and biological markers of infection. These include chronic obstructive pulmonary disease (COPD) patients that show the highest expansion in the number of reported cases over the past decade.[3–8] COPD is a pulmonary disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Four stages of COPD are defined from mild, moderate, severe, to very severe (stages I to IV, respectively).[9] Airway colonization by *Aspergillus* spp. is a common feature in chronic lung diseases.[10] Although cumulative factors that trigger lung invasiveness are not completely understood, the leading concern remains when and how appropriate antifungal treatment should be initiated. This issue is critical considering the poor outcome unanimously reported in the literature of COPD patients suffering from IPA.[5,6]

Voriconazole is a synthetic antifungal agent belonging to the triazoles chemical family. Voriconazole has regulatory approval for primary treatment of IPA and has been recommended for use as the initial therapy for patients with this disease.[2,11] This review provides an overview of the use of voriconazole and the particular aspects that have to be taken in consideration in the setting of COPD. This includes the need to refer to pathophysiological processes underlying IPA and to diagnostic issues that we will discuss as decisive supports for antifungal treatment initiation.

Epidemiology

An accurate estimation of IPA incidence in COPD patients is difficult, partly due to the lack of infection surveillance measures. In a study including 595 patients with IPA, 9% suffered from nondetailed pulmonary diseases.[12] In a review including 50 studies of aspergillosis case-fatality rate, COPD was the underlying condition in 26 out of 1941 patients (1.3%) with aspergillosis.[13] Several autopsy studies from intensive care unit (ICU) patients confirm that invasive fungal diseases (IFD) are among the most commonly missed diagnoses.[14,15] Taken together, these studies suggest that IPA incidence amongst COPD patients may be underestimated. Higher risk of IPA occurrence may be correlated with advanced stages of COPD. As reported in a recent series of 57 probable IPA, 36 patients (63.2%) were stage III and 21 (33.8%) were stage IV.[16] The global mortality rate of IPA in COPD patients reported in the literature is high, ranging from 72% to 95%.[5,6,16] This makes a sharp contrast with the latest outcome data from hematopoietic stem cell transplant recipients, where a clear trend toward a drop in attributable mortality has been observed in recent years (from 60%–70% to 40%).[17]

Pathophysiology

Aspergillus spp. are airborne fungi that undergo a biphasic-growth process. Spores or conidia, which represent the form of environmental persistence and dissemination, are inhaled during breathing and their small size (2–3 μm) allows them to reach the lung alveoli. Conidia germinate to produce branching and septate filaments known as hyphae (~2 to 10 μm in diameter), which are the invasive form responsible for tissue damage. Upper respiratory tract clearance of inhaled conidia is facilitated by tracheobronchial ciliary activity. Conidia are ingested and destroyed by airway macrophages that prevent germination to hyphal form. Germinating spores and hyphae are attacked by polymorphonuclear neutrophils (PMNs) through the release of oxidants and degranulation. Pulmonary dendritic cells ingest both conidia and hyphae, migrate to draining lymph nodes and instruct the T helper-cell response.[18]

The development of IPA in COPD patients is due to combined factors. First, nutritional depletion is prevalent in advanced COPD and clinical research has provided evidence that undernutrition in advanced COPD is associated with an increased mortality, notably related to lung infections.[19] A second factor is the impairment of ciliary function by chronic tobacco smoke and multiple episodes of infection reduce microbial pathogens clearance from lung airways.[9] Third, the use of broad-spectrum antibiotics in case of exacerbations affects the distribution of normal flora, which may lead to a shift toward development of fungal populations in airways. Furthermore, a recent study showed that *A. fumigatus* has the ability to grow as a biofilm *in vivo* which may enable chronic persistence within lungs and promote antimicrobial resistance.[20] This is of significant concern for COPD patients in ICU with synthetic devices in lung airways (eg, endotracheal tube). Finally, corticosteroids have significant impact on the distribution and function of neutrophils, monocytes, and lymphocytes.[21,22] They also directly stimulate the growth of *A. fumigatus in vitro* possibly *via* the sterol binding protein in the fungus.[23] Thus, intravenous (IV) corticosteroids treatment in COPD patients appears to be associated with a

rising incidence of IPA. Some reports also describe that high doses of inhaled corticosteroids may promote the occurrence of IPA.[24–26]

In summary, COPD is characterized by significant variability in local immune balance that impacts the patient ability to contain invasive fungal challenges over time. Taken together, the intrinsic progression of the disease characterized by an increasing rate of microbial colonization, the exacerbations of viral and bacterial origins, the repetitive use of antibiotics, the necessity of occasional admissions in ICU with the requirement for invasive procedures, the steroid-induced immunomodulation, and the sepsis-related cycling fluctuations of immune status from hyper- to anti-inflammatory phases (that can confine to immunoparalysis in extreme cases)[27] create favorable conditions for the development of opportunistic invasive mould infections such as IPA.

Clinical features

The diagnosis of IPA in nonneutropenic patients is difficult because signs and symptoms are nonspecific such as fever, increased respiratory secretions, dyspnea exacerbation and high oxygen requirements, persistent bronchospasm despite elevated doses of corticosteroids. The occurrence of hemoptysis is less reported in COPD patients than in hematological patients. In the context of evolving COPD, persistent rapid-developing infiltrative abnormalities on thoracic imaging and/or persistent pulmonary infection despite broad-spectrum antibiotics should trigger further investigations focused on fungal infection.

Assessing the diagnosis of IPA in COPD patients

Baseline criteria

The definitions have assigned three levels of probability for the diagnosis of IPA: proven, probable, and possible. Proven IPA can apply to any patient, regardless of whether the patient is immunocompromised, on the common basis that histopathological documentation of infection and/or a culture positive specimen from a normally sterile site is required. This usually involves use of invasive procedures to obtain tissue specimens which is rarely feasible, especially in COPD patients.

In 2007, an attempt to standardize definitions of IPA in COPD patients was proposed by Bulpa and colleagues that established a formal framework based on previously published information.[5] The classification focused on advanced stages of COPD (stages III and IV). The collection of hyphae in a lung biopsy specimen remained the decisive argument for proven IPA. For probable and possible IPA, the recommendation was given to rely on a combination of criteria taking into account nonspecific changes on chest computed tomography (CT) imaging, positive cultures from lower respiratory tract and positive biological markers such as serum antibody and/or antigen tests.

Definitions of IFD in immunocompromised patients have been recently revised.[28] Aside from proven IPA, the definition of probable and possible IPA in immunocompromised patients is based on a combination of less-specific criteria within three categories: host factors, clinical manifestations (symptoms, signs, and radiological features), and mycological evidence. Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host and a clinical criterion but for which mycological evidence lacks are considered possible IFD. In this revised definition of IFD it has to be taken into account that predisposing host factors were extended to receipt of immunosuppressive agents including prolonged use of corticosteroids, which is often the case in COPD patients. However, the revised definitions do not apply to critically ill patients in the ICU who, nonetheless, may include COPD patients that develop probable or possible IPA.

Diagnostic procedures

Lung biopsy

Establishing the presence of fungi in tissue gives the highest level of certainty in diagnosing IPA. Transthoracic percutaneous needle aspiration, video-assisted thoracoscopic biopsy, or transbronchial biopsies are standard procedures to obtain histopathological evidence of IPA that reveals characteristic angular dichotomously branching septate hyphae on direct microscopic examination and/or *Aspergillus* spp. on culture. A yield in the range of 50% has been reported for percutaneous biopsy needle, which indicates that a negative result should not rule out the diagnosis.[29] However, the invasiveness of these procedures exposes COPD patients to severe respiratory and/or bleeding complications.

Microbiological examination

Sputum

Direct examination of sputum can be rapidly performed and is reported to be positive for *Aspergillus* in half of all IPA cases.[30] The use of fluorescence techniques optimizes the yield of microscopic examination up to 80%–90%.[31]

Based on literature data, the significance of positive sputum cultures for *Aspergillus* in COPD patients developing

pneumonia is not clearly established. From a practical point of view, the possibility of IPA has to be taken into consideration in each case of advanced steroid-dependant COPD in patients experiencing antibiotic-resistant pneumonia. The recovery of several positive culture samples in a row in the course of such an ongoing pneumonia is clearly evocative of the diagnosis. In that case, further investigations must be triggered if possible and concern about antifungal treatment must be raised.

Fiberoptic flexible bronchoscopy

Fiberoptic flexible bronchoscopy with sampling of deep airway secretions and bronchoalveolar lavage (BAL) allows samples to be collected that can be processed for microscopic examination, fungal culture, and antigen or molecular detections. It has to be taken into account that BAL might be difficult to obtain in patients with low respiratory status due to advanced COPD. The macroscopic visualization of ulcerative lesions and/or pseudomembranes is suggestive of *Aspergillus*-related infection. The yield of culture positive specimens has ranged from 46% to 77%.[30,32–35] BAL is more often positive in cases of prolonged pneumonia or extensive pulmonary lesions.

In summary, the isolation of *Aspergillus* spp. from the respiratory tract of a COPD patient with pneumonia confronts to two possibilities: colonization or current invasive disease. BAL is the technique that may provide the wider range of information through direct visualization of bronchial tree, and collection of distal samples. But BAL is often difficult to perform. Therefore, the diagnosis is more likely to rely on positive culture of sputum and bronchoaspirates. The positive predictive value for IPA of repeatedly positive sputum or bronchoaspirate cultures for *Aspergillus* spp. in advanced COPD patients must not be underestimated in the context of antibiotic-resistant pneumonia.

Biological markers

Detection of antibodies

A positive serum antibody test for *A. fumigatus* remains one of the biological criteria proposed for the diagnosis of IPA in COPD according to Bulpa and colleagues.[5] However, an increase in antibodies directed toward *Aspergillus* spp. requires a functional immune status and a pattern of infection long enough to generate a significant antibody response. Long-term steroid-dependant COPD patients are likely to develop weaker antibody responses and brief courses of IPA often do not allow seroconversion and the follow-up of kinetic antibody responses.

Antibody detection is more likely used in diagnosis of chronic pulmonary aspergillosis for which it is reported that high titers of antibodies are more common in more seriously ill patients, and generally would increase during exacerbations.[36] On this basis, the monitoring of titers to detect the passage of chronic semi-invasive disease to invasive disease might be useful.

Serological techniques

The development of nonculture-based diagnostics has focused on the detection of surrogate markers for *Aspergillus* spp., such as the galactomannan (GM) antigen, [1→3]-β-D-glucan and the detection of *Aspergillus* DNA by polymerase chain reaction (PCR).

GM is a major *Aspergillus* cell-wall component that is released during the hyphal growth phase. It is used as an exo-antigen for the purpose of *Aspergillus* detection.[37] The GM serum assay has been extensively investigated in immunocompromised patients. A meta-analysis including 27 studies regarding the value of the GM serum assay for surveillance of IPA in hematological and solid-organ transplant recipient patients ultimately revealed a moderate accuracy for diagnosis of IPA with various median sensitivity and specificity: for proven cases alone, which were 71% and 89% respectively; combining proven and probable cases, which were 61% and 93%, respectively.[38] The test is more useful in patients who have hematological malignancy or who have undergone hematopoietic cell transplantation than in solid-organ transplant recipients. The use of GM assay for the diagnosis of IPA in patients with COPD might be very limited. A retrospective study which enrolled critically ill patients without malignancy, 27% of whom were COPD patients, is worth mentioning:[39] the diagnostic value of the GM assay demonstrated a sensitivity of only 53% in patients with proven or probable IPA (cut-off value of 1 ng/mL). This indicates clearly that data from patients with malignancies and after solid organ transplantation cannot be extrapolated to other critical conditions. In the largest series available of IPA in COPD patients, 44% of the 34 patients tested were positive (cut-off value of 0.5 ng/mL).[16] The low sensitivity of GM in serum of these patients with values in a range of 40%–55% is a major limitation.

Because GM is a water-soluble carbohydrate, it can also be detected in BAL fluid. In small clinical studies among patients with hematological malignancies and solid organ transplant recipients, the sensitivity of the GM assay applied to BAL fluids ranges from 85% to 100% (cut-off value of 1.5 ng/mL).[40–43] A recent prospective study conducted in ICU

patients, of whom 8% were COPD patients, the sensitivity and specificity of GM detection in BAL fluid was 88% and 87%, respectively (cut-off value of 0.5 ng/mL).[44] Consequently, there is an increasing tendency to use these samples for diagnosis of IPA despite the fact that the assay is not specifically validated for detection of GM in this fluid.

Several circumstances can be source of false-positives for the GM antigen test in either serum or BAL fluid. First, the false-positive reactivity can be caused by gastro-intestinal translocation of fungal GM from contaminated food or drink,[45] or by the use of the intravenous antibiotics piperacillin–tazobactam and amoxicillin–clavulanic acid.[46,47] Second, an important factor that affects the release of GM antigens is antifungal drug therapy. Different animal and human studies have shown decreased sensitivity of the GM assay when using prophylactic antifungal drugs.[48,49]

The [1→3]-β-D-glucan is a cell wall component of many filamentous fungi and yeasts, including *Aspergillus* and *Candida* species. Reproducible assay results, with high specificity and a high positive predictive value, demonstrated that use of an assay to detect serum [1→3]-β-D-glucan derived from fungal cell walls might be a useful diagnostic adjunct for invasive fungal infection.[50] A single case of positive [1→3]-β-D-glucan values during fatal IPA in a COPD patient has been reported which indicated a value increase at day 15 over the course of a 21 days-illness.[51] In addition, false-positive tests have been found in patients after hemodialysis, cardiopulmonary bypass surgery, high-dose immunoglobulin treatment, after exposure to glucan-containing gauze, and in cases of bacterial infections among ICU patients.[52,53] Hence, the usefulness of [1→3]-β-D-glucan in the diagnosis of IPA has clearly to be further evaluated.

Amplification of nucleic acid by PCR technology for the diagnosis of IPA is being increasingly studied. Yet, it is not included in the definitions of IPA due to the lack of standardization. It can be applied to serum and BAL specimens.[54–59] Experience is still limited and a recent meta-analysis yielded a sensitivity and specificity for two consecutive positive samples of 75% and 85%, respectively.[60] However, most of studies were done in the hematological setting. Therefore, the role of PCR in patients with COPD is mostly unknown. As for the GM assay, there are factors that potentially have an impact upon the clinical sensitivity of PCR: the magnitude of the quantitative PCR signal decreases with antifungal therapy, potentially causing false-negative PCR results.[61] The colonization of the respiratory tract by *Aspergillus* spp. may suggest a low positive predictive value.[56] Finally, patients at risk for IPA are often prescribed a multitude of drugs and fluids, all of which may act as nonspecific inhibitors of the PCR. For example, anticoagulants inhibit PCR, thereby limiting its sensitivity.[62]

In summary, the use of GM, [1→3]-β-D-glucan tests, and *Aspergillus* PCR as serological and molecular markers cannot be wisely advocated for routine use in COPD patients, and caution is warranted in the interpretation of positive test results in patients without a clinical suspicion of pulmonary infection and negative test results in patients with persisting pneumonia. The finding of sequentially positive GM tests in serum or BAL fluid together with a positive *Aspergillus* PCR, in a patient with persisting pulmonary infection who carries one or more risk factors, is highly indicative for IPA and would justify considering antifungal therapy.

Radiology

Chest CT is an important tool for the diagnosis of IPA in neutropenic patients. CT has been proven effective in the absence of evident lesions on a conventional chest X-ray. Radiological findings might include nodules with rapid growth and/or cavitations. A "halo sign" (corresponding to a pulmonary mass surrounded by a zone of lower attenuation with ground-glass opacification produced by adjacent hemorrhage) and/or the "air crescent sign" (corresponding to crescentic radiolucencies around a nodular area of consolidation) may be present.[63–71]

However, thoracic imaging in mechanically ventilated ICU patients is less helpful due to many confounding factors such as atelectasis and, sometimes major, pleural effusions. A lower sensitivity (from 5% to 24%) of the halo sign and air crescent sign in non-neutropenic patients has been reported in the literature.[39,72,73] In the study by Guinea and colleagues, the worsening of imaging data is one of the five independent variables suggestive of IPA in patients with COPD and clinical isolation of *Aspergillus* spp. from lower respiratory samples.[16]

Antifungal therapy

In 2002, a large randomized trial reported an improved response and survival rate for patients with IPA who received therapy with voriconazole compared with patients who received standard deoxycholate amphotericin B therapy (so far, liposomal formulations of amphotericin B and voriconazole have not been compared in clinical trials for the treatment of IPA). This led to the recommendation to use voriconazole as the primary treatment of IPA.[74] However, this study included 277 patients but only 16 were receiving corticosteroids as predisposing conditions; the majority of

the remaining patients had hematological malignancies. Therefore, the evidence of the superiority of voriconazole over amphotericin B for the treatment of IPA in patients with COPD cannot be inferred from this study. Furthermore, rather conflicting data are available in experimental models. In a model of lethal infection in guinea pigs, two studies concluded that voriconazole therapy at 10 mg/kg/day prolonged survival compared to that of guinea pigs treated with conventional amphotericin B at 1 and 1.25 mg/kg/day, respectively.[75,76] Another recent study concluded that the efficacy of high dose liposomal amphotericin B (at 5 and 10 mg/kg) was superior to that of voriconazole (10 mg/kg) in a mouse model of pulmonary aspergillosis.[77] Obviously, there is an urgent need for adequately-designed prospective clinical trials comparing voriconazole to conventional and/or liposomal formulation of amphotericin B in nonimmunocompromised high-risk patients, COPD inclusively.

Voriconazole is a synthetic triazole compound that exerts an inhibitory effect on two kinds of *Aspergillus* cytochrome P450-dependant enzymes: the first enzyme targeted is lanosterol 14-α-demethylase that participates in ergosterol biosynthesis. Inhibition of this enzyme results in altered cell membrane function. The second group of targeted enzymes belongs to the fungal respiration chain. Their inhibition limits cell growth and replication and ultimately leads to cell death. Triazoles are generally considered as fungistatic.

Voriconazole is formulated as tablets or as sulfobutyl-ether cyclodextrin (SEC) solution for IV administration. SEC and voriconazole dissociate in plasma. As SEC is renally cleared and consequences of its plasma accumulation are still uncertain, caution is advised when using the IV formulation in patients with renal impairment (creatinine clearance $<$50 mL/min).[2,78] This concern does not apply to orally administrated voriconazole.

The oral formulation has 90% to 96% bioavailability. The absorption is better when administered either one hour before or after a meal. No formal relationship has been established between body weight and kinetics justifying the fixed dose in adult patient $\geq$40 kg. Voriconazole is mostly hepatically metabolized, with only 5% of the drug appearing unchanged in the urine. The elimination half-life of ~6 hours warrants twice-daily dosing. Voriconazole is biotransformed by cytochrome P450-dependant isoenzymes CYP2C19, CYP2C9, and CYP3A4 acting as both a substrate and an inhibitor of these isoenzymes. This extensive and saturable hepatic metabolism explains the nonlinear pharmacokinetic profile of voriconazole in adults, with maximum concentration in plasma and area under the curve increasing disproportionally with increasing dose. Once voriconazole concentrations start approaching or exceeding the saturation level of the enzyme, small increases in the voriconazole dose will result in much larger increases in the drug concentration.[79,80] Thus, intra- and interpatient voriconazole concentrations in serum may vary considerably depending on age, drug dose, concurrent illness, underlying liver function, drug-to-drug interactions, or genetic polymorphisms affecting cytochrome CYP2C19-mediated metabolism.[78,81] Single-nucleotide polymorphisms contributing to slow metabolism are represented in ~3% of white Europeans and in higher frequencies, from 15% to 20%, among non-Indian Asian populations.[82] An analysis that attempted to determine the relationship between voriconazole plasma concentrations and abnormal liver function test values, indicated that the risk of developing elevated liver function test values increased by 7% to 17% for every 1 μg/mL increase in the random voriconazole concentration.[83] As no threshold was found, the investigators argued that therapeutic drug monitoring of voriconazole concentrations is not more helpful in predicting abnormal liver function test values than measuring liver function directly. Another recent study emphasizes that therapeutic drug monitoring of voriconazole improves the efficacy and safety of therapy in severely ill patients with invasive mycoses. Among the 52 enrolled patients, a large variability in voriconazole trough blood levels was observed, ranging from $<$1 mg/L (the minimum inhibitory concentration at which, for most fungal pathogens, 90% of isolates are susceptible) to $>$5.5 mg/L (the potentially toxic threshold).[84] Lack of response to therapy was more frequent in patients with low voriconazole levels $<$ 1 mg/L (six patients, five of whom had IPA) than in those with voriconazole levels above that limit. In these patients, blood levels $>$1 mg/L were reached after increasing the voriconazole dosage, with resolution of infection meaning that patients subsequently responded to therapy after their voriconazole daily dose was increased without the addition of a second antifungal to the treatment regimen. This result suggests that, although pharmacokinetic variability is a factor possibly contributing to the poor clinical outcome, dosage of voriconazole allows the correction of suboptimal serum levels. Among 16 patients with voriconazole trough blood levels $>$ 5.5 mg/L, five patients presented with neurological toxicity. In all cases, discontinuation of therapy resulted in prompt and complete neurological recovery. Thus, detection of voriconazole trough levels outside the therapeutic interval of 1–5.5 mg/L during the first week of therapy may help prevent treatment failures and anticipate the occurrence of drug-related toxicity.

Voriconazole diffuses widely in tissues with an emphasis on CSF levels which can reach up to 50% of plasma levels. Pharmacokinetics of voriconazole has been studied in

conditions that might be relevant with COPD status:[85] delivery of voriconazole by a jejunostomy twice daily appears feasible whether tablets are crushed or not. Consistently, nasogastric administration through nasogastric tube can be an alternative option to IV injection for mechanically ventilated patients although cautious has to be raised on intact intestinal absorption in this category of patients. Consequently, patient medications should be reviewed for drug interactions. Briefly, the main drugs that potentially increase voriconazole concentrations are erythromycin, indinavir, ranitidine, cimetidine, and omeprazole. Drugs that potentially decrease voriconazole concentrations are principally rifampicin (probably rifabutin as well) and phenytoin. Kinetics of other co-administrated drugs such as cyclosporine, digoxin, and phenytoin may be notably altered by voriconazole which implies adapting the dosages of some of these drugs based on the determination of their blood concentrations.[85]

Voriconazole's profile of adverse reactions include transient visual disturbances (principally photopsia), hepatotoxicity (elevated serum bilirubin, alkalin phosphatase, and hepatic aminotransferase enzyme levels) which may be dose limiting, and skin rash usually in sunlight-exposed areas. Visual and auditory hallucinations have been reported, mainly occurring upon receipt of initial loading doses.[86] Other side effects have been reported such as confusion, and pneumonitis.[81,87]

Treatment of IPA with voriconazole in adults is initiated with a loading dose of 6 mg/kg IV every 12 hours for two doses on the first day, followed by 4 mg/kg every 12 hours; ultimate oral dosage is 200 mg every 12 hours. Primary combination therapy is not routinely recommended based on the lack of clinical data. Addition of another agent or switch to another drug class for salvage therapy may be considered in individual patient cases. Duration of therapy for most conditions associated with IPA has not been optimally defined. Duration should be from admission to treat until resolution or stabilization of all clinical and radiologic manifestations. Reversal of immunosuppression, if feasible, is important for a favorable outcome. The question whether long-term steroid treatment should be maintained, decreased, or interrupted should be addressed.

Conclusion

There are still many questions that need to be addressed and understood in the diagnosis and treatment of IPA in COPD patients. The high mortality rate is partly related to the delays in diagnosis and treatment because of non-specific symptoms and difficulties to meet gold standard criteria. A persistent pulmonary infection despite broad-spectrum antibiotics associated with abnormal CT thoracic imaging should trigger further investigations focused on moulds. Tissue biopsy evidencing *Aspergillus* spp. on microscopic examination or in culture is the gold standard but is difficult to obtain. Culture and microscopy of respiratory tract samples obtained by fiberoptic flexible bronchoscopy with sampling of deep airway secretions and BAL have an overall sensitivity and specificity of around 50%. Combining noncultured-based diagnostic tools in serum and/or BAL (eg, PCR and GM or GM and [1→3]-β-D-glucan) is an important research direction that may improve the overall predictive value of these systems in patients. Antifungal therapy may be considered in COPD patients with rapidly progressive antibiotic-resistant pneumonia and should be started in that case when cultures for *Aspergillus* spp. or sequentially positive GM (in serum or BAL) are positive. The antifungal triazole voriconazole is recommended to be the first line treatment of IPA despite the lack of specific data in COPD patients. Based on the nonlinear metabolic elimination of this drug, a follow-up of voriconazole blood levels may be useful during the first week of therapy.

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Disclosure

The authors declare no conflicts of interest in this work.

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