



## Case report

# Issues in the management of invasive pulmonary aspergillosis in non-neutropenic patients in the intensive care unit: A role for isavuconazole



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## ABSTRACT

**Background:** Almost half of all cases of invasive aspergillosis (IA) occur in the intensive care unit (ICU), with mortality rates of 70–80% for probable or proven cases. IA has become a major concern among non-neutropenic patients in the ICU with chronic obstructive pulmonary disease (COPD) but although prompt, appropriate antifungal therapy is crucial, diagnosis in this situation is challenging. Criteria for a probable diagnosis in critically ill patients have been proposed to help to expedite therapy.

**Methods:** A case of probable invasive pulmonary aspergillosis (IPA) in a non-neutropenic patient admitted to the ICU was used to illustrate potential issues in the diagnostic work-up and management of patients in this setting.

**Results:** A non-neutropenic 69-year-old man with COPD receiving clomipramine was diagnosed in the ICU with probable invasive aspergillosis based on the presence of severe chronic obstructive pulmonary disease, suspected X-linked granulomatous disease, nodular infiltrates and galactogamman positivity on bronchoalveolar lavage (BAL) fluid. Voriconazole was unsuitable due to the patient's prolonged QT interval and risk of a drug–drug interaction with clomipramine. Isavuconazole was initiated and the patient's condition improved. The three-month course of isavuconazole treatment was well-tolerated and resulted in complete recovery of the patient.

**Conclusions:** Voriconazole is a standard first-line treatment for IA but intravenous therapy is associated with toxicity and the potential for drug–drug interactions. Isavuconazole is another first-line therapy which was effective and safe in the management of this critically ill non-neutropenic patient with baseline QT prolongation and potential drug–drug interactions with voriconazole.

## Introduction

Invasive fungal infections in the intensive care unit (ICU) are often missed or diagnosed late due to non-specific signs and symptoms, a low index of suspicion, and the difficulty of differentiating between colonization and infection [1]. However, invasive infections caused by filamentous fungi are potentially devastating.

Almost half of all cases of invasive aspergillosis (IA), the most frequent invasive fungal infection [1], occur in the ICU [2]. Estimates of the incidence of IA in critical care units range from 0.3% to 19% [3]. Patients with IA in the ICU are often referred with pre-existing infection, for example after developing respiratory failure in the bone marrow transplant unit due to IA. Alternatively, patients who acquire IA in the community or as a nosocomial infection may be admitted directly to the ICU while, less often, patients may acquire IA while in the ICU due to airborne spores in contaminated air. Reported mortality rates following diagnosis of proven or probable IA are extremely high: proven or probable IA in the ICU can lead to death in over 70–80% of

cases, largely due to delayed diagnosis [4].

In recent years, IA has become a major concern among non-neutropenic patients with a mild degree of immunosuppression and without classic predisposing risk factors [4]. The most common underlying comorbidities in non-neutropenic patients are chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome, chronic corticosteroid therapy, liver cirrhosis, congenital or acquired immunodeficiency, and recent thoracic or valvular surgery. Prompt, appropriate antifungal therapy in IA is crucial to improve clinical outcomes and reduce mortality. However, achieving a proven diagnosis of IA in non-neutropenic patients is challenging, since clinical manifestations (e.g. fever, cough and purulent sputum) are non-specific, and the conventional radiologic features of “halo sign” and “air crescent sign” are present in only a minority of non-neutropenic patients.

Starting therapy at the stage of possible infection, as opposed to proven or probable infection, might improve survival rates [5]. Voriconazole is a first-line treatment for IA according to current guidelines

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[6] and is widely used. However, voriconazole has been associated with an increased risk for adverse events, including renal impairment in patients given intravenous therapy, hepatotoxicity, reversible ocular disturbances, photosensitivity, exfoliative dermatitis, cutaneous reactions, neurotoxicity and QT prolongation [7,8]. Moreover, since voriconazole is metabolized by human P450 cytochromes, it has the potential for drug–drug interactions in patients receiving other P450-CYP3A4 substrates [9].

Isavuconazole is a novel triazole agent with a wide spectrum of antifungal activity. It is recommended as a first-line therapy for IA in recent guidelines from the European Conference on Infections in Leukemia (ECLL) [10] and the Infectious Diseases Society of America (IDSA) [11] based on the results of the phase III SECURE study which demonstrated non-inferiority to voriconazole [12]. The main advantages of isavuconazole compared to voriconazole are: (1) reduced nephrotoxicity in patients given intravenous therapy; (2) it does not contribute to a prolonged QT interval; (3) fewer drug–drug interactions; and (4) no requirement for dose adjustments in patients with renal or hepatic impairment [12,13].

The following case report illustrates some potential issues in the diagnostic work-up and management of patients admitted to the ICU with probable invasive pulmonary aspergillosis (IPA).

## Case report

### Clinical presentation

A 69-year-old man with severe COPD requiring chronic oxygen supplementation (1 L/min) and suspected underlying X-linked granulomatous disease was admitted to the ICU with acute-on-chronic respiratory failure. He had a progressively worsening cough, shortness of breath, increased sputum production and had experienced a 10 kg weight loss with muscle depletion in the preceding three months. The patient had been treated for pulmonary tuberculosis at the age of 23 years, with no subsequent recurrence of infection. Chronic treatment with clomipramine (75 mg/day) was ongoing for a major depressive syndrome which had been diagnosed five years earlier. He was being monitored with monthly serial electrocardiograms for QT prolongation attributable to clomipramine therapy.

### Diagnosis of invasive pulmonary aspergillosis

At ICU admission, the patient presented with severe dyspnea. Arterial blood-gas analysis showed mixed respiratory failure (pH 7.22, PaO<sub>2</sub> 58 mmHg, PaCO<sub>2</sub> 80 mmHg, HCO<sub>3</sub><sup>−</sup> 35 mMol/L) requiring non-invasive ventilation. Chest examination revealed bilateral crackles, with no signs of chronic heart failure. Blood tests showed the white blood cell count to be in the normal range (8000/mm<sup>3</sup>), with no neutropenia (neutrophil count 1846/mm<sup>3</sup>), but mild lymphopenia was present (lymphocytes 810/mm<sup>3</sup>). The patient was anemic (Hb 10.9 g/dL). Platelet count was high (438,000/μL) and C-reactive protein (CRP) was markedly increased (35 mg/L; normal level < 5 mg/L). Renal function was normal (serum creatinine 0.9 mg/dL), as were liver function tests (aspartate transaminase [AST] 11 IU/L, alanine transaminase [ALT] 14 IU/L, gamma-glutamyl transpeptidase [GGT] 30 IU/L, total bilirubin 0.15 mg/dL). Baseline electrocardiogram showed a sinus rhythm with a right bundle branch block and prolonged QT interval (453 ms).

Chest x-ray showed multiple bilateral lung opacities. CT and [18F] fluorodeoxyglucose (FDG)-PET/CT scans revealed bilateral nodular infiltrates.

Due to the patient's critical condition and the multiple potential etiologies for the pulmonary infection, a bronchoscopy was performed, which demonstrated purulent secretions. Broncho-alveolar lavage (BAL) fluid was negative for bacteria, fungi, mycobacteria, *Actinomyces* spp. and *Nocardia*, but tested positive for galactomannan (GM; ODI

2.6).

According to the European Organisation for Research and Treatment of Cancer (EORTC) criteria for non-neutropenic patients [6], the diagnosis of probable IPA was made based on the presence of baseline predisposing comorbidities (severe COPD and suspected X-linked granulomatous disease), the presence of bilateral nodular infiltrates, and GM positivity on BAL.

### Treatment

Voriconazole was considered unsuitable due to the patient's baseline QT prolongation and the risk of a drug–drug interaction with clomipramine, potentially leading to further QT prolongation and severe cardiac arrhythmias. Isavuconazole therapy was selected, and started with a loading dose of 200 mg every 8 h for six doses, following by 200 mg daily.

### Outcome

After starting antifungal treatment with isavuconazole, the patient showed a progressive improvement in his clinical condition. At week 2, the arterial blood-gas analysis showed resolution of the decompensated respiratory acidosis, with normalization of pH (pH 7.40, PaO<sub>2</sub> 62 mmHg, PaCO<sub>2</sub> 50 mmHg, HCO<sub>3</sub><sup>−</sup> 30 mMol/L). There was no further need of non-invasive ventilation. On day 17, the patient was moved from the ICU to the infectious diseases ward, and required only low flow oxygen supplementation (1 L/min). He was discharged on day 42. CT scanning and FDG-PET/TC after eight weeks of antifungal treatment confirmed the improvement of pulmonary infiltrates. In total, a three-month course of isavuconazole treatment was completed, and there were no clinical or radiologic signs of infection after six months' follow-up. Isavuconazole was well-tolerated, with no adverse events and no change in liver enzymes. Serial ECG monitoring showed no prolongation of the QT interval.

## Discussion

Invasive fungal diseases have been categorized as proven, probable or possible by the EORTC/MSG Consensus Group [6]. Proven diagnosis of IA requires confirmation by histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy [6], which inevitably involves a delay. Criteria for a probable diagnosis in critically ill patients have been proposed [14] that can help to expedite therapy. These require a lower respiratory tract specimen culture positive for *Aspergillus*, compatible signs and symptoms, abnormal medical images of the lungs by X-ray or CT scan, with either host risk factors or a semi-quantitative *Aspergillus*-positive culture of BAL fluid and detection of branching hyphae on cytological smear [14]. GM positivity on BAL fluid, in particular, has high sensitivity (87%) and specificity (87%) for the diagnosis of IA [15]. In our patient, these criteria were met and the findings were also consistent with probable IPA according to EORTC/MSG criteria [6].

Voriconazole is a standard first-line treatment for proven or probable IA and is widely prescribed [6]. However, our patient was receiving the tricyclic antidepressant clomipramine which can increase the QT interval (likely accounting for the prolonged QT interval in this patient), and addition of voriconazole could compound this risk. A recent retrospective study by Gueta et al. analyzed risk factors associated with QT prolongation in a cohort of hemato-oncologic patients treated with voriconazole [16]. Baseline QT prolongation (≥ 450 ms) and low serum potassium levels were found to be independent risk factors for a prolonged QT interval [16]. Moreover, an increased risk has been observed when voriconazole is administered in combination with other drugs which can induce QT prolongation (e.g. fluoroquinolones and methadone), potentially resulting in life-threatening arrhythmias such as “torsade de pointes” [17,18]. Contrasting results were found in a

*post-hoc* analysis of data from patients receiving isavuconazole in the SECURE trial [12]. The analysis demonstrated that the 50% inhibitory concentrations for L-type  $\text{Ca}^{2+}$  channels were higher than the maximum serum concentrations of non-protein-bound isavuconazole *in vivo*. As a result, isavuconazole does not prolong the QT interval. Indeed, isavuconazole is associated with a shortened QT interval, which leads to its contraindication in patients with familial short QT syndrome [13,19], a rare (100 reports in the literature to date) genetic disorder characterized by accelerated repolarization and a predisposition for cardiac arrest [20]. Here, another option might have been to change clomipramine to an alternative agent with a lower risk for QT prolongation.

Voriconazole inhibits multiple enzymatic pathways and is a substrate and inhibitor of multiple cytochromes including CYP2C19, CYP2C9, CYP3A4 and CYP2B6 [21], increasing its potential for drug–drug interactions with CYP inhibitors and inducers. Clomipramine is metabolized by CYP2C19, and a possible interaction could not be ruled out. The effect of different triazoles on the cytochrome P450 system varies; isavuconazole shows less extensive drug–drug interactions than voriconazole and only interactions with CYP3A4 inducers or inhibitors are of concern [19].

Mortality from IA in the critical care setting exceeds 70%, and this patient had a particularly poor prognosis due to his comorbid COPD and X-linked chronic granulomatous disease. Prompt initiation of antifungal treatment was essential due to the patient's critical condition, but voriconazole was contraindicated due to the increased risk of QT interval prolongation. The case described here shows that isavuconazole is effective and safe in the management of a critically ill non-neutropenic patient with baseline QT prolongation and potential drug–drug interactions with voriconazole.

### Competing interests

Matteo Bassetti has received research grants from Astellas, Pfizer, MSD and Gilead, has acted as an advisor/consultant to Angelini, Astellas, AstraZeneca, Bayer, Basilea, Gilead, Menarini, MSD, Pfizer, Novartis, Shionogi, Vifor, The Medicines company, Tetrphase, Achaogen and Paratek, and has received speaker's honoraria from Angelini, Astellas, AstraZeneca, Bayer, Pfizer, MSD, Gilead, Vifor, Novartis, Bayer and Tetrphase.

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### References

- [1] Bassetti M, Bouza E. Invasive mould infections in the ICU setting: complexities and solutions. *J Antimicrob Chemother* 2017;72(suppl. 1):39–47.
- [2] Cornillet A, Camus C, Nimubona S, Gandemer V, Tattevin P, Belleguic C, et al.

- Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: a 6-year survey. *Clin Infect Dis* 2006;43(5):577–84.
- [3] Dimopoulos G, Frantzeskaki F, Poulakou G, Armaganidis A. Invasive aspergillosis in the intensive care unit. *Ann NY Acad Sci* 2012;1272:31–9.
- [4] Meersseman W, Vandecasteele SJ, Wilmer A, Verbeke E, Peetermans WE, Van Wijngaerden E. Invasive aspergillosis in critically ill patients without malignancy. *Am J Respir Crit Care Med* 2004;170(6):621–5.
- [5] Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Amé S, Fohrer C, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis* 2008;47(9):1176–84.
- [6] De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. European organization for research and treatment of Cancer/Invasive fungal infections cooperative group. revised definitions of invasive fungal disease from the european organization for research and treatment of Cancer/Invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORT/MSG) consensus group. *Clin Infect Dis* 2008;46(12):1813–21.
- [7] Dolton MJ, McLachlan AJ. Voriconazole pharmacokinetics and exposure-response relationships: assessing the links between exposure, efficacy and toxicity. *Int J Antimicrob Agents* 2014;44(3):183–93.
- [8] Epaulard O, Leccia MT, Blanche S, Chosidow O, Mamzer-Bruneel MF, Ravaud P, et al. Phototoxicity and photocarcinogenesis associated with voriconazole. *Med Mal Infect* 2011;41(12):639–45.
- [9] Groll AH, Townsend R, Desai A, Azie N, Jones M, Engelhardt M, et al. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P 450 3A4. *Transpl Infect Dis* 2017(July). <http://dx.doi.org/10.1111/tid.12751>. 19. Epublication ahead of print.
- [10] Herbrecht R, Tisot F, Agrawal S, et al. Update of the ECIL guidelines for antifungal treatment in leukemia and HSCT patients. 2013. <http://www.kobe.fr/ecil/telechargements2013/ECIL5%20Antifungal%20Therapy.pdf>.
- [11] Patterson TF, Thompson 3rd GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016;63(4):e1–60.
- [12] Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet* 2016;387(10020):760–9.
- [13] Keirns J, Desai A, Kowalski D, Lademacher C, Mujais S, Parker B, et al. QT interval shortening with isavuconazole: in vitro and in vivo effects on cardiac repolarization. *Clin Pharmacol Ther* 2017;101(6):782–90.
- [14] Blot SI, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselsaers N, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. *Am J Respir Crit Care Med* 2012;186(1):56–64.
- [15] Meersseman W, Lagrou K, Maertens J, et al. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. *Am J Respir Crit Care Med* 2008;177(1):27–34.
- [16] Gueta I, Loebstein R, Markovits N, Kamari Y, Halkin H, Livni G, et al. Voriconazole-induced QT prolongation among hemato-oncologic patients: clinical characteristics and risk factors. *Eur J Clin Pharmacol* 2017;73(9):1181–5.
- [17] Zeuli JD, Wilson JW, Estes LL. Effect of combined fluoroquinolone and azole use on QT prolongation in hematology patients. *Antimicrob Agents Chemother* 2013;57(3):1121–7.
- [18] Prosser JM, Mills A, Rhim ES, Perrone J. Torsade de pointes caused by poly-pharmacy and substance abuse in a patient with human immunodeficiency virus. *Int J Emerg Med* 2008;1(3):217–20.
- [19] Cresemba Prescribing Information, Basilea Pharmaceutica International Ltd (June 2015).
- [20] Mazzanti A, Kanthan A, Monteforte N, et al. Novel insight into the natural history of short QT syndrome. *J Am Coll Cardiol* 2014;63(13):1300–8.
- [21] Jeong S, Nguyen PD, Desta Z. Comprehensive in vitro analysis of voriconazole inhibition of eight cytochrome P450 (CYP) enzymes: major effect on CYPs 2B6, 2C9, 2C19, and 3A. *Antimicrob Agents Chemother* 2009;53(2):541–51.