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# Invasive pulmonary aspergillosis post extracorporeal membrane oxygenation support and literature review

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ABSTRACT

The use of extracorporeal membrane oxygenation (ECMO) for reversible pulmonary failure in critically ill patients has increased over the last few decades. Nosocomial infections are a major complication of ECMO and fungi have been found to be a common cause. Herein, we describe a case of invasive pulmonary aspergillosis following ECMO, which was successfully treated with combination antifungal therapy and interferon-gamma.



## 1. Introduction

The use of extracorporeal membrane oxygenation (ECMO) for intensive care patients with severe cardiac or reversible pulmonary failure has become more common over the last 30 years [1]. Complications resulting from ECMO further increase the mortality in this group of patients, which is already high due to severity of underlying illness [2]. After haemorrhage, infection is the second most common complication of ECMO, with reports of up to 45% of patients being affected [2,3]. Fungi such as *Candida* have been found to be a common cause of infection in this group [4]. We describe a case where ECMO was employed as a part of the management of severe community acquired pneumonia (CAP) and the patient developed an invasive pulmonary infection with *Aspergillus fumigatus*. This is the first case to describe successful treatment with combination antifungal therapy and interferon-gamma. This case report also highlights the difficulty in diagnosing invasive pulmonary aspergillosis (IPA), the importance of monitoring voriconazole levels in the blood and of careful consideration of antifungal drug interactions with other medication.

## 2. Case

A 48 year-old male presented with a 7-day history of cough, shortness of breath and diarrhoea. His past medical history included hypertension, chronic obstructive pulmonary disease (COPD) and diet-controlled diabetes. Furthermore, he had worked as a welder and was an ex-smoker. He was initially treated with amoxicillin and steroids by his general practitioner but after 4 days his symptoms worsened which led to hospital admission (day 0). He presented with severe sepsis. Blood tests showed an increase in the markers of infection (C-reactive protein and total white cell count were 279mg/L and $21.9 \times 10^9$/L respectively) and he had a base excess of $-19.3$. A chest radiograph revealed right-sided consolidation. A diagnosis of severe CAP was made and a course of intravenous amoxicillin-clavulanate and clarithromycin was started. Unfortunately, he rapidly developed multi-organ failure including type II respiratory failure and further deteriorated resulting in a peri-arrest situation. He was therefore intubated and transferred to the intensive care unit (ICU) where he received sustained low-efficiency dialysis (SLED). A computed tomography (CT) scan of his chest showed dense consolidation throughout his right lung, with cavitations in the right upper lobe (day +1). A bronchoalveolar lavage (BAL) grew *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Haemophilus influenza*. His antibiotic therapy was changed to a combination of piperacillin–tazobactam, linezolid and clindamycin. He was given two doses of intravenous immunoglobulin for suspected Panton Valentine Leukocidin *S. aureus* (later found to be negative). Other tests including blood cultures, respiratory viral PCR, culture and PCR for *Mycobacterium tuberculosis* on BAL samples, culture of CT-guided aspirate from lungs, atypical pneumonia serology screen, stool culture and *Legionella* antibody and urinary antigen were all negative. His condition worsened despite high frequency oscillatory

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ventilation and therefore he was referred for consideration of, and ultimately transferred for, ECMO at another tertiary centre (day +4). On day +22, he was transferred back to our ICU after his condition improved, but he remained critical. He had persistent pyrexia despite treatment with linezolid and ciprofloxacin, with fluconazole prophylaxis. A repeat CT scan of his chest revealed a large abscess in the right lung (Fig. 1). A CT scan of the head showed 1.5 cm lesions in the thalamus, basal ganglia and frontal lobe, which were thought to be either fungal infection or haemorrhage secondary to ECMO. *A. fumigatus* was grown from BAL and an endotracheal aspirate (ETA) and he was started on amphotericin B (amBisome) increasing to 5 mg/kg and other antibiotics were stopped (day +24).

A repeat BAL grew *Serratia marcescens* and *A. fumigatus* so he was restarted on piperacillin–tazobactam (day +31). A further ETA grew *S. aureus* therefore flucloxacillin, clindamycin, and rifampicin were added. Repeat BAL grew more *S. aureus* and *A. fumigates* (day +34). The patient remained pyrexial and unable to be weaned from ventilatory support. On day +37, a chest drain was inserted into the intra-pulmonary abscess under CT guidance. Cultures grew profuse *A. fumigatus* sensitive to posaconazole, itraconazole, voriconazole, amphotericin, and caspofungin. Voriconazole was added to amBisome (day +39) after a 2-week course of the latter due to the well recognised penetration of this agent into brain tissue. His liver function deteriorated, possibly due to an interaction between rifampicin and voriconazole. Moreover, concomitant rifampicin and voriconazole are contra-indicated as the former is known to reduce the exposure of voriconazole by more than 90% by inducing cytochrome P450 so rifampicin was stopped. A repeat ETA aspirate grew *Klebsiella oxytoca* and *Enterobacter cloacae* (day +58). Gentamicin was added and he had a further course of piperacillin–tazobactam. Aspergillus PCR on blood was negative but this does not preclude a diagnosis of invasive aspergillosis (day +60). Trans-oesophageal echocardiography was performed due to ongoing pyrexia and it ruled out endocarditis. Toxoplasma serology and HIV testing were carried out and both were negative. The patient was found to be anaemic, lymphopaenic, and thrombocythaemic (day +72). Investigations for immune compromise were carried out, particularly as the patient had been well prior to his admission, multiple organisms had grown on culture and disease had remained severe despite appropriate antifungals and antibiotics. A bone marrow aspirate showed no changes attributable to lymphoma however plasma B cells were abnormally low. His IgG was 22.20 g/L, which was appropriately elevated and compatible with infection. IgA was 6.73 g/L (moderately elevated) and IgM 0.80 g/L, which was normal. Lymphocyte subsets were normal apart from a low CD 19 (B cell) count of $15 \times 106$/L. A CT scan did not show changes suggestive of lymphoma. These investigations suggested functional immune impairment and the patient was not responding to treatment. After discussion with immunologists and a thorough literature search a course of interferon-gamma was initiated (day +82). After 3 weeks of voriconazole and 5 weeks of amBisome, ETAs were still yielding *A. fumigatus*. Following expert mycologist advice amBisome was discontinued, and the patient started anidulafungin (day +93) whilst continuing voriconazole. We aimed to have voriconazole levels more than 1 mg/L but less than 6 mg/L and the levels were regularly monitored. Low trough voriconazole levels of $< 0.1$ mg/L were found, probably due to the prior exposure to rifampicin, so we increased the dose from 200 mg b.d. to 300 mg b.d. After this, voriconazole levels remained around 1.8 mg/L. Mycology experts advised a minimum of 12 weeks of antifungal therapy. Following this, a CT chest and head revealed that abscesses and lesions were decreasing in size. Blood samples were taken and although serum *Aspergillus* galactomannan was not detected the β-1,3 glucan level was 115 pg/mL which was above the 80 pg/mL cut-off for positivity. Cardiothoracic surgeons reviewed the patient for consideration of pulmonary abscess excision, but they did not feel intervention was feasible. A particularly resistant *Enterobacter cloacae* grew from chest samples and antibiotics were changed to meropenem and then ciprofloxacin and he finished 6 weeks of flucloxacillin. Flucloxacillin was restarted for 2 weeks only a month later (day +118), and then again after another 2 weeks as *S. aureus* grew from blood cultures, peripherally inserted central catheter (PICC line) tip and sputum. He remained on anidulafungin and voriconazole and on day +150 in ICU CT imaging showed chest and brain lesions were further reducing in size. Anidulafungin was stopped after 4 months and the patient was switched to oral voriconazole after 5 months, with a plan to continue this for long-term maintenance along with flucloxacillin. He was discharged to the medical high dependency unit (MHDU) after +166 days on ICU. He was then transferred to a respiratory ward and made progress before transfer to a rehabilitation ward and then discharged home. Currently the patient has no chest symptoms or confusion, can walk with a stick but has some residual weakness. He remains on flucloxacillin 500 mg b.d and voriconazole 300 mg b.d.

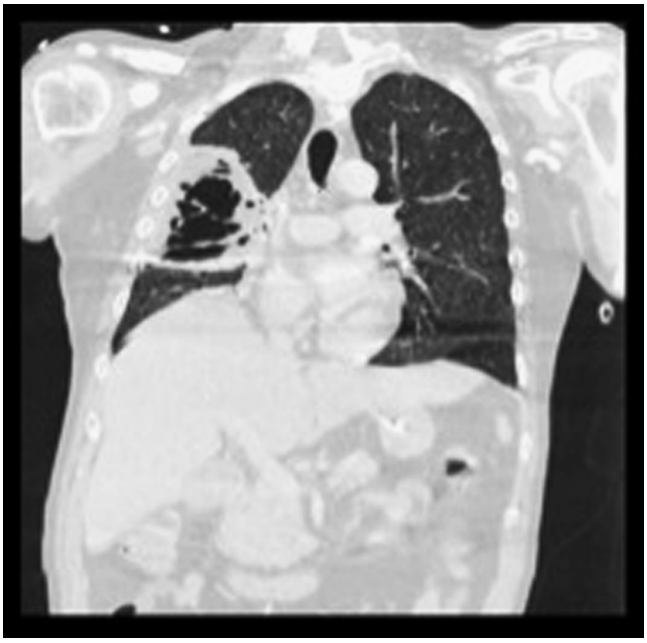

**Fig. 1.** CT chest scan showing large intrapulmonary collection posterolaterally in right upper lobe measuring up to 14.5 cm with multiloculated gas and fluid. There is collapse consolidation of basal right lower lobe.

## 3. Discussion

*Aspergillus* is a ubiquitous environmental hyaline mould. Typically, invasive aspergillosis affects patients who are immunocompromised such as patients with inherited immunodeficiencies, advanced HIV infection, prolonged neutropenia and allogeneic hematopoietic stem cell transplantation (HSCT) [5]. Aspergillosis is also an emerging opportunistic infection in critically ill patients in the ICU, particularly in patients with COPD or severe liver disease [6]. Over the last three decades the use of ECMO for the management of life threatening pulmonary or cardiac failure (or both) has increased. Prolonged ECMO use has been identified as a risk factor for ECMO-related nosocomial infection [2,7]. Patients are at risk of nosocomial infection whilst on ECMO as they have multiple portals of entry [2,8]. Fungi such as *Candida* have been identified as a common cause of infection in this group [4,9].

We report a case of putative IPA in a patient following ECMO treatment. The diagnosis of IPA is generally difficult to make in critically ill patients. There is revised guidance on categorising IPA written by the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) in which a proven diagnosis needs histopathologic evidence of fungal invasion [10,11]. This is meant as guidance on the security of different diagnostic procedures in determining the likelihood of disease rather than a diagnostic guideline. In ICU patients, diagnosing IPA from histological specimens is difficult for many reasons. It is common for open lung biopsy to be contraindicated due to coagulation disorders or severe respiratory failure as in our case. Additionally, radiological findings in ventilated patients can be non-specific and galactomannan antigen detection on serum may not be useful in patients who are not neutropenic. An alternative clinical algorithm has been developed for the diagnosis of putative invasive pulmonary aspergillosis in ICU patients [11]. In our patient, the negative galactomannan test did not preclude the diagnosis of pulmonary infection. A galactomannan antigen test carried out on the CT guided BAL fluid may well have had greater diagnostic value. Once the brain lesions had been discovered it may have been diagnostically useful to perform galactomannan, beta-glucan and PCR tests on CSF samples, however in this case it would not have altered the management as disseminated aspergillosis was already considered the most likely cause. In our patient the positive β-1,3 glucan was indicative of invasive fungal infection but due to its almost pan-fungal detection was not able to determine the pathogen. Moreover, there have been reports of false positive reactions in patients receiving amoxicillin-clavulanate or piperacillin–tazobactam, both of which had been used in this patient, and also cross-reactions in gram negative bacteraemia.

The first case report of invasive aspergillosis in a patient on ECMO was described in an infant in 2012 [6]. It was diagnosed on autopsy, which showed fluid filled lungs, necrosis and angioinvasive septated hypha with dichotomous branching most likely to be due to an *Aspergillus* species. The authors also carried out a retrospective analysis of the Extracorporeal Life Support Organization (ELSO) registry data looking at the outcomes of 46 adult and paediatric cases of *Aspergillus* infection and colonisation. They found that *Aspergillus* infection/colonisation was associated with a 70% overall mortality in patients receiving ECMO and that it often occurred in hosts who did not have known immunodeficiencies. They did not distinguish between infection and colonisation in these patients or describe how they made the diagnosis. An Australian series from 2005 to 2011 reported their experience of treating these patients. They described ECMO patients who had *Aspergillus* isolated from clinical specimens, examining their characteristics and outcome [1]. *A. fumigatus* was the most common species isolated and many patients did not have 'classic' underlying risk factors (neutropenia, steroids, immunodeficiency, immunosuppressive therapy). The in-hospital mortality rate was found to be 74%. They used the alternative clinical algorithm that has been developed for the diagnosis of putative invasive pulmonary aspergillosis in ICU patients [11]. They identified two cases of putative IPA as well as one case of proven IPA. Using the modified criteria, we classified the first reported case as a proven IPA and our case as a putative case as we were unable to take a histology sample. It is interesting to note that most cases had suffered a cardiac arrest as did our case (Table 1).

Our patient was managed with combination therapy and interferon-gamma. Once the brain lesions had been recognised we were keen to use voriconazole due to its good penetration into CSF. He made particularly good progress when amphotericin was switched to anidulafungin whilst he remained on voriconazole. This regime is not routinely recommended by IDSA guidance

**Table 1**
Reported cases of invasive pulmonary aspergillosis secondary to ECMO.

| Citation | Age, Sex | Reason for ECMO | Cardiac Arrest before ECMO | Sample type and tests | Evidence of *Aspergillus* | Treatment | Diagnosis | Outcome |
|---|---|---|---|---|---|---|---|---|
| [6] | 6 week old, M | ARDS septic shock | Yes | Histology of lungs on autopsy | Hyphae consistent with *Aspergillus* spp. and necrosis | Not treated | Proven IPA | Died |
| [1] | 63 year old, F | Lung Transplant | Yes | BAL BA | *A. fumigatus* culture | Voriconazole | Putative IPA | Died |
| [1] | 35 year old, F | ARDS pneumonia | No | BAL lung biopsies | *A. fumigatus* culture | AmBisome | Proven IPA | Died |
| [1] | 44 year old, M | Heart Transplant | Yes | BAL | *A. fumigatus* hyphae | Not treated | Putative IPA | Died |
| This report | 48 year old, M | ARDS pneumonia | Yes | BAL ETA | *A. fumigatus* culture | AmBisome Voriconazole Anidulafungin (Long term Voriconazole) | Putative IPA | Alive |

BAL – bronchoalveolar lavage, BA – bronchial aspiration, ARDS – acute respiratory distress syndrome, ETA – endotracheal aspirate, IPA – invasive pulmonary aspergillosis.

[12]. This guidance advises that IPA should be treated with voriconazole as a first line agent, however another agent could be added or a switch to another drug class could be made in cases in which salvage therapy is necessary [12]. There is little clinical data for combination therapy and also conflicting results from studies [13–16] Of note, a recent study has shown that combination of voriconazole and anidulafungin is synergistic in voriconazole-susceptible invasive aspergillosis [17]. We added in interferon-gamma after discussion with immunology experts, as there is some evidence of impaired production of interferon-gamma in patients with chronic pulmonary aspergillosis. Again there is little data on the benefits of its use apart from case reports of successful treatment in transplant patients not responding to antifungal therapy [18,19]. This includes two patients with cerebral fungal infection (mortality 90%), who both made a full recovery. Current guidelines on the treatment of aspergillosis written by the Infectious Diseases Society of America also refer to its role as an adjunctive anti-fungal therapy for invasive infection in immunocompromised non-neutropenic patients, particularly those with chronic granulomatous disease [12]. We felt our patient would also benefit from long-term voriconazole treatment. There is limited data on the benefits of long-term treatment with antifungals but after discussion with expert mycologists treatment with voriconazole was continued. Recently a study examining long-term antifungal treatment over a period of 12 months demonstrated an improvement in the health status of patients and prevention of chronic pulmonary aspergillosis progression in some patients [20].

Patients undergoing ECMO are at increased risk of infections compared to other patients in ICU (3). Clinicians should consider infection with fungus in patients not responding to antibiotics. From our literature review, we found that ECMO patients with IPA did not always have 'classic' underlying risk factors. We also found that most cases had suffered a cardiac arrest. Diagnosing IPA in ICU patients can be difficult but a clinical algorithm to diagnose IPA in these patients can be useful. Thought should be given to using combination antifungal therapy and/or interferon-gamma on an individual patient basis in certain IPA cases. Clinicians should also monitor voriconazole levels in the blood to guide dosing, and be aware of antifungal drug interactions and side-effects. In our case the concomitant use of rifampicin may well have contributed to initially low voriconazole levels as it is well recognised that this agent is an inducer of cytochrome P450 (CYP450) leading to more rapid metabolism of voriconazole. Repeat imaging and sampling can be useful to assess response to antifungals. Long-term antifungal treatment may need to be considered after discharge from the ICU.

## Conflict of interest statement

Elizabeth Johnson has received research funding and/or honoraria from Pfizer, Gilead Sciences, Astellas and Merck.

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