SHORT COMMUNICATION

Aspergillus sp. isolated in critically ill patients with extracorporeal membrane oxygenation support

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Abstract
This study reports Aspergillus isolation in critically ill patients who underwent extracorporeal membrane oxygenation (ECMO) and highlights the difficulty in establishing a diagnosis of aspergillosis in this population. The diagnosis of Aspergillus infection or colonization was retrospectively performed using the proposed modified criteria of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) adapted to critically ill patients. Between 2005 and 2011, 11 of 151 patients (7.2%) who underwent ECMO had Aspergillus sp. isolates, 10 in a pulmonary sample and 1 in a mediastinal wound sample. Five patients did not have any classical risk factors for aspergillosis. One patient had a proven invasive pulmonary aspergillosis (IPA), 2 had a putative IPA, and 1 patient had a possible Aspergillus mediastinitis, whilst in 7 patients this was considered colonization. However, the clinical relevance of Aspergillus isolation was based on an algorithm not validated in patients undergoing ECMO. Our data support the need to implement non-invasive diagnostic procedures for aspergillosis in this population.

Keywords: Aspergillus sp., extracorporeal membrane oxygenation, critically ill patients

Introduction
Recent data suggest that aspergillosis is an emerging disease in critically ill patients, with an incidence of invasive aspergillosis ranging between 0.3% and 5.8% [1–4]. Most importantly, half of these cases are not associated with immunosuppressive therapy or with neutropenia, which are the well-recognized predisposing factors for invasive aspergillosis [2–5]. When isolated in intensive care unit (ICU) patients, Aspergillus sp. is often of uncertain clinical significance, as a definitive diagnosis is difficult to establish. The diagnostic approach usually involves radiological imaging and/or a biopsy, but critically ill patients may be difficult to transport for radiological investigations and often have coagulopathy that precludes invasive diagnostic procedures. The European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) guidelines for the diagnosis of aspergillosis do not have diagnostic criteria for invasive aspergillosis in non-neutropenic critically ill patients [6,7]. Nevertheless, given that there is no consensus regarding the definition of the diagnostic criteria for ICU patients, non-invasive methods such as galactomannan detection [8] have proved to be reliable and diagnostic algorithms [1,9] have been developed to help intensivists with diagnosis. Establishing a timely diagnosis is necessary for early initiation of antifungal treatment, which is important because aspergillosis is an independent predictor of death in ICU patients and is associated with a high mortality [2,10,11].

Extracorporeal membrane oxygenation (ECMO) is a rescue therapy that has become increasingly common over the last decades for reversible
life-threatening cardiac and respiratory failure [12,13]. Nosocomial infections are a major complication of ECMO and may negatively impact on outcome [14–17]. Furthermore, in a few studies, fungi were amongst the main isolated pathogens [14,16,18]. Recently, Garcia et al. reported a paediatric case of invasive aspergillosis acquired when the patient was on ECMO. They also compared adult and paediatric cases of Aspergillus infection requiring ECMO support among the cohort of the Extracorporeal Life Support Organization (ELSO) registry [19]. However, they did not provide details of how the diagnosis of aspergillosis was made and they did not discuss the significance of Aspergillus isolation in these patients [19].

We report a single-centre experience of ECMO patients who had Aspergillus isolated from clinical specimens. We describe their characteristics and outcome and note the clinical difficulties in assessment.

Methods

Design

This study was a retrospective single-centre cohort study conducted over 6.5 y in the ICU of the Alfred Hospital, a quaternary referral hospital in Melbourne, Australia. The 30–35-bed ICU has had an average of 1900 admissions a year over the last 5 y and operates an ECMO referral service in the southern Australian states of Victoria and Tasmania. The Alfred Hospital also provides lung and heart transplantation and oncology and haematology services. This study was conducted with the approval of the Alfred Health Human Research Ethics Committee.

Patients and data

All patients who underwent ECMO between January 2005 and June 2011 and who had a first microbiological sample with Aspergillus during ECMO support were enrolled. Specimens for culture were taken at the discretion of the treating clinician and no systematic screening procedures were performed. Demographic data, including sex, age, underlying diseases, immunosuppressive therapy, and corticosteroids were collected. The following data related to the ICU stay and ECMO were recorded: main ECMO indication, APACHE II score (Acute Physiology And Chronic Health Evaluation) [20] at admission, ICU admission and discharge dates, ECMO initiation and cessation dates, type of ECMO (veno-venous or veno-arterial), the SOFA score (Sequential Organ Failure Assessment) before ECMO deployment [21], renal replacement therapy requirement, and occurrence of cardiac arrest before ECMO. The date of isolation and type of microbiology sample from which Aspergillus was isolated were recorded. The results of chest X-rays and of chest computed tomography (CT) scans (where performed) were analysed and recorded by 2 of the investigators blinded to the outcome (DP and AC). Finally, the administration of antibiotic therapy and the presence of other infective agents at the same time were collected.

Case definition

Patients were classified as having proven, probable, possible, or putative invasive pulmonary aspergillosis (IPA) or Aspergillus colonization, based on the EORTC/MSG criteria and an alternative clinical algorithm adapted for critically ill patients from these criteria and recently validated [9]. Briefly a proven IPA was defined with a positive histology or culture on sterile material. A probable IPA was defined by the 3 following criteria: presence of host factors, signs suggestive of invasive aspergillosis on chest CT scan, and mycological criteria. A possible IPA was defined by the presence of host factors and suggestive signs on chest CT scan. A putative IPA was defined by the association of the 4 following criteria: Aspergillus-positive lower respiratory tract specimen culture, compatible clinical signs and symptoms, abnormal medical imaging (chest X-ray, chest CT scan), and either host factors or semi-quantitative Aspergillus-positive culture of bronchoalveolar lavage (BAL) fluid without bacterial growth and with branching hyphae on the cytology smear. The case was classified as Aspergillus tract colonization when one of the criteria for putative IPA was missing [9]. No indirect method such as galactomannan in BAL or plasma was used at the Alfred Hospital.

Statistical analysis

Data were analysed descriptively. All statistical analyses were performed using Stata 10.0 (College Station, TX, USA). Categorical variables were compared between groups with the Fisher’s exact test and continuous variables were compared with the Mann–Whitney U-test for non-parametric data. The incidence of Aspergillus isolation in patients undergoing ECMO was compared with the incidence in all critically patients for the same study period.

Results

During the study period, 11 of the 151 patients who received ECMO had a microbiological Aspergillus-positive culture. This rate of 7.2% is substantially
higher than the incidence of Aspergillus isolated in the 9379 ICU admissions (1.7%) over the same period.

Cases are described in Tables I and II. They had a median of age of 48 y (interquartile range (IQR) 43.5–59.5 y), were more often male (7/11), and had a median APACHE II score at ICU admission of 19 (IQR 15–30). Four patients (36%) experienced a cardiac arrest before ECMO initiation and 8 required renal replacement therapy (RRT) (72%). The median SOFA score calculated the day of ECMO initiation was 14.5 (IQR 12–17). Only 1 patient was not on broad-spectrum antibiotic therapy when Aspergillus was isolated.

Almost half of the patients (5/11) did not have any classical host risk factors for Aspergillus disease, including neutropenia, immunodeficiency, corticosteroid therapy, and immunosuppressive therapy. None were neutropenic, although 1 patient was treated 2 days before Aspergillus diagnosis with granulocyte colony-stimulating factor (G-CSF) for a neutrophil count under 500/mm³. Aspergillus was isolated from the respiratory tract in 10 of 11 cases, with a single additional case of Aspergillus isolated from the mediastinal wound. One patient had histological testing to support the diagnosis of definite IPA; 2 patients had a putative IPA and 7 patients were considered respiratory tract colonization according to the alternative clinical algorithm published by Blot et al. [9]. No post-mortem diagnosis of aspergillosis was performed in any patient. Aspergillus fumigatus was isolated in 10 of the 11 cases. Antifungal therapy was initiated in 7 patients and consisted of voriconazole for 2 patients, Ambisome or amphotericin B for 4 patients, and caspofungin in 1 case. In patients for whom imaging was available, the chest X-ray and chest CT scan showed nonspecific anomalies, but in 3 patients the changes were not explained by another cause (Table II).

Eight patients were successfully weaned off ECMO, however 4 died subsequently at the hospital; the overall in-hospital mortality of the patients with Aspergillus isolation was 74% (100% in the non-colonized patients and 42% in patients with respiratory tract colonization), while the overall mortality of all patients who underwent ECMO for more than 48 h during the study period was 34.2%. The median SOFA score at ECMO initiation for patients with Aspergillus was also significantly higher than that of the overall ECMO population (14.5, IQR 12–17 vs 12, IQR 10–14; p = 0.02). Interestingly, immunodeficiency was not associated with an increased risk of death when compared with the overall ECMO population (mortality of 30%), and the mortality of patients with cardiogenic shock other than following surgery was 40%.

Discussion

This study suggests that ICU patients undergoing ECMO may be especially susceptible to Aspergillus. Our results show that Aspergillus may not necessarily be associated with immunosuppressive therapies and neutropenia in critically ill patients. It also highlights the difficulty of establishing the clinical relevance of Aspergillus isolation in this group of patients and the poor prognosis with which Aspergillus is associated.

Reports vary as to the burden of aspergillosis in the ICU [1–4]. However, the rate of Aspergillus isolation reported in ECMO patients in the current study (7.2%) is higher than those reported in heterogeneous ICU populations [3,4]. Regardless of this difference in incidence, our population shares many similarities with ICU patients from whom Aspergillus was isolated. Almost half of our patients were not immunosuppressed as defined traditionally, many of them had severe organ dysfunction with a high baseline SOFA score, and almost a third experienced a cardiac arrest. These findings are in accordance with reports suggesting that severe organ dysfunction is a risk factor for Aspergillus [10]. In addition, most of them received broad-spectrum antibiotic therapy, which has also been identified as a risk factor for fungus infection [3,10]. A. fumigatus was isolated in more than 90% of cases [3,22]. Aspergillus isolation associated with the ECMO procedure has rarely been reported and has generally involved mediastinitis, particularly in heart transplant patients [14,18]. Garcia et al. recently described a case of angioinvasive Aspergillus infection in an infant who underwent ECMO. They also reported 46 cases of Aspergillus in 20,741 patients undergoing ECMO, making the incidence of Aspergillus 0.22% [16,19]. This incidence is far lower than in our cohort and the authors did not provide details and the significance of Aspergillus isolation in accordance with the EORTC/MSG guidelines. However, the mortality in that study is as high as the mortality of our patients, confirming the poor prognosis of patients on ECMO with Aspergillus isolation [19].

Determining the clinical significance of Aspergillus isolation in this patient population is difficult. Aspergillus may be associated with disease through a number of mechanisms, including invasive disease, allergic bronchopulmonary aspergillosis, obstructive bronchial aspergillosis, and pulmonary aspergilloma. Our study illustrates the considerable difficulty in diagnosing aspergillosis in ECMO patients. Clinical symptoms and radiological signs may be both insensitive as well as non-specific (particularly as ECMO may be initiated for respiratory disease), and biopsies to obtain a histological diagnosis are hazardous because of the need for anticoagulation. Comparison
Table I. Patient and extracorporeal membrane oxygenation characteristics.

<table>
<thead>
<tr>
<th>Case</th>
<th>Date of Aspergillus isolation</th>
<th>Gender</th>
<th>Age, y</th>
<th>ECMO indication</th>
<th>APACHE II score</th>
<th>Type of ECMO</th>
<th>Days in ICU before ECMO</th>
<th>Cardiac arrest before ECMO</th>
<th>SOFA before ECMO</th>
<th>RRT</th>
<th>Associated antibiotic therapy</th>
<th>Other pathogens isolated simultaneously</th>
<th>Diagnostic conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>February 2010</td>
<td>M</td>
<td>60</td>
<td>Heart Tx (0–7)</td>
<td>22</td>
<td>VA central</td>
<td>0</td>
<td>No</td>
<td>6</td>
<td>No</td>
<td>—</td>
<td>Enterobacter cloacae; Klebsiella pneumoniae</td>
<td>Colonization</td>
</tr>
<tr>
<td>2</td>
<td>May 2010</td>
<td>M</td>
<td>19</td>
<td>CM/FM</td>
<td>32</td>
<td>VA peripheral</td>
<td>0</td>
<td>Yes</td>
<td>14</td>
<td>Yes</td>
<td>Ticarcillin–clavulanic acid; gentamicin</td>
<td>—</td>
<td>Colonization</td>
</tr>
<tr>
<td>3</td>
<td>October 2010</td>
<td>M</td>
<td>46</td>
<td>CM/FM</td>
<td>34</td>
<td>VA peripheral</td>
<td>0</td>
<td>Yes</td>
<td>18</td>
<td>Yes</td>
<td>Ticarcillin–clavulanic acid</td>
<td>—</td>
<td>Colonization</td>
</tr>
<tr>
<td>4</td>
<td>June 2009</td>
<td>M</td>
<td>48</td>
<td>ARDS–H1N1</td>
<td>19</td>
<td>VV</td>
<td>6</td>
<td>No</td>
<td>17</td>
<td>Yes</td>
<td>Vancomycin; meropenem</td>
<td>—</td>
<td>Colonization</td>
</tr>
<tr>
<td>5</td>
<td>February 2008</td>
<td>F</td>
<td>59</td>
<td>CM/FM</td>
<td>40</td>
<td>VA peripheral</td>
<td>1</td>
<td>No</td>
<td>17</td>
<td>Yes</td>
<td>Vancomycin; ciprofloxacin; vancomycin</td>
<td>—</td>
<td>Colonization</td>
</tr>
<tr>
<td>6</td>
<td>May 2008</td>
<td>F</td>
<td>63</td>
<td>Lung Tx (0–7)</td>
<td>16</td>
<td>VA peripheral</td>
<td>0</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Vancomycin; cefepime; meropenem</td>
<td>—</td>
<td>Putative IPA</td>
</tr>
<tr>
<td>7</td>
<td>June 2008</td>
<td>M</td>
<td>56</td>
<td>Heart Tx (0–7)</td>
<td>28</td>
<td>VA central</td>
<td>0</td>
<td>No</td>
<td>12</td>
<td>No</td>
<td>Vancomycin; ciprofloxacin; ceftriaxone</td>
<td>Enterococcus faecium in wound, mediastinum, and blood</td>
<td>Probable mediastinum aspergillosis</td>
</tr>
<tr>
<td>8</td>
<td>September 2008</td>
<td>F</td>
<td>35</td>
<td>ARDS–pneumonia</td>
<td>14</td>
<td>VV</td>
<td>8</td>
<td>No</td>
<td>12</td>
<td>No</td>
<td>Meropenem; vancomycin</td>
<td>—</td>
<td>Proven IPA</td>
</tr>
<tr>
<td>9</td>
<td>December 2007</td>
<td>F</td>
<td>63</td>
<td>Heart Tx (0–7)</td>
<td>19</td>
<td>VA central</td>
<td>4</td>
<td>No</td>
<td>15</td>
<td>Yes</td>
<td>Vancomycin; ciprofloxacin; meropenem</td>
<td>—</td>
<td>Colonization</td>
</tr>
<tr>
<td>10</td>
<td>June 2005</td>
<td>M</td>
<td>43</td>
<td>CM/FM</td>
<td>12</td>
<td>VA central</td>
<td>1</td>
<td>No</td>
<td>18</td>
<td>Yes</td>
<td>Ticarcillin–clavulanic acid</td>
<td>Meropenem; tobramycin; vancomycin</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>June 2005</td>
<td>M</td>
<td>44</td>
<td>Heart Tx (0–7)</td>
<td>13</td>
<td>VA central</td>
<td>3</td>
<td>Yes</td>
<td>13</td>
<td>Yes</td>
<td>—</td>
<td>Putative IPA</td>
<td>—</td>
</tr>
</tbody>
</table>

APACHE II score, Acute Physiology And Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; CM/FM, cardiomyopathy/fulminant myocarditis; ECMO, extracorporeal membrane oxygenation; F, female; Heart Tx (0–7), heart transplantation in the last 7 days; H1N1, influenza H1N1; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; Lung Tx (0–7), lung transplantation in the last 7 days; M, male; NA, not available; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; VA central ECMO, veno-arterial ECMO with a mediastinal access to right atrium and aorta; VA peripheral, veno-arterial ECMO with a femoro-femoral access; VV, veno-venous ECMO.
Table II. Criteria for aspergillosis diagnosis and patient outcomes.

<table>
<thead>
<tr>
<th>Case</th>
<th>Histology</th>
<th>Host factors</th>
<th>Compatible clinical signs</th>
<th>Leukocyte and lymphocyte counts</th>
<th>Days between ECMO and Aspergillus isolation</th>
<th>Chest X-ray features suggestive of or likely to be associated with Aspergillus</th>
<th>Mycology criteria</th>
<th>Diagnostic conclusion</th>
<th>Antifungal treatment</th>
<th>ECMO outcome</th>
<th>Hospital outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>12,930/μl 350/μl</td>
<td>3</td>
<td>No (basal shadows/effusion R &gt; L, progressively improved)</td>
<td>A. fumigatus (BA)</td>
<td>Colonization</td>
<td>Voriconazole</td>
<td>Successful weaning</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>−</td>
<td>+</td>
<td>22,360/μl 3700/μl</td>
<td>5</td>
<td>No (bilateral infiltrates progressively improved until death)</td>
<td>A. fumigatus (BAL)</td>
<td>Colonization</td>
<td>Not treated</td>
<td>Successful weaning</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>−</td>
<td>+</td>
<td>13,300/μl 1220/μl</td>
<td>0</td>
<td>No (dense bilateral consolidation which progressively improved)</td>
<td>A. fumigatus (BA)</td>
<td>Colonization</td>
<td>Not treated</td>
<td>Successful weaning</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>NA</td>
<td>−</td>
<td>+</td>
<td>35,500/μl 1150/μl</td>
<td>1</td>
<td>Yes (bilateral patchy infiltrate, which deteriorated for 2 days, then stable for 4 days following Aspergillus isolation)</td>
<td>A. fumigatus (BAL)</td>
<td>Colonization</td>
<td>Amphotericin B</td>
<td>Never weaned</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>13,400/μl 870/μl</td>
<td>10</td>
<td>No (initially R then L side infiltrate, possible cavitation on L and then Aspergillus isolated while the chest X-ray was improving and continued to improve after this)</td>
<td>A. fumigatus (BA)</td>
<td>Colonization</td>
<td>Not treated</td>
<td>Successful weaning</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>14,200/μl 2330/μl</td>
<td>8</td>
<td>Yes (bilateral infiltrates R &gt; L, then worse on L with haemothorax, which was drained; the chest X-ray improved then deteriorated)</td>
<td>A. fumigatus (BAL and BA)</td>
<td>Putative IPA</td>
<td>Voriconazole</td>
<td>Successful weaning</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>9870/mm³ 570/mm³</td>
<td>14</td>
<td>No (minor bifasal infiltrate after drainage of L effusion on day 1, L haemothorax on final day)</td>
<td>A. fumigatus (mediastinum)</td>
<td>Possible mediastinum aspergillosis</td>
<td>Amphotericin B</td>
<td>Successful weaning</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>1640/mm³ 1720/mm³</td>
<td>1</td>
<td>Yes (dense bilateral pulmonary infiltrate)</td>
<td>A. fumigatus (BAL, lung biopsies)</td>
<td>Proven IPA</td>
<td>Ambisome</td>
<td>Never weaned</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>4610/mm³ 190/mm³</td>
<td>5</td>
<td>No (minor R basal shadowing initially, progressively improved)</td>
<td>A. niger (BA)</td>
<td>Colonization</td>
<td>Ambisome</td>
<td>Successful weaning</td>
<td>Died</td>
</tr>
<tr>
<td>10</td>
<td>NA</td>
<td>−</td>
<td>+</td>
<td>10,430/mm³ 420/mm³</td>
<td>1</td>
<td>No (initially L then R basal infiltrate which progressively improved)</td>
<td>A. fumigatus (BA)</td>
<td>Colonization</td>
<td>Caspofungin</td>
<td>Successful weaning</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>26,000/mm³ 420/mm³</td>
<td>4</td>
<td>Yes (initially clear, then developed R haemothorax then worsening bilateral, posterior and R upper consolidation)</td>
<td>A. fumigatus (BAL) hyphae</td>
<td>Putative IPA</td>
<td>Not treated (brain death)</td>
<td>Bridge weaning</td>
<td>Died</td>
</tr>
</tbody>
</table>

BA, bronchial aspiration; BAL, bronchoalveolar lavage; ECMO, extracorporeal membrane oxygenation; IPA, invasive pulmonary aspergillosis; L, left; NA, not available; R, right.

*Host factors' means immunodeficiency.

Patient neutropenic (390/mm³), who received granulocyte colony-stimulating factor 48 h before.
of the rate of colonization and definite or probable/possible disease with literature data is difficult because there is no consensus on the appropriate definition of invasive aspergillosis in ICU patients [1,2,10]. For instance, some authors consider only a lower respiratory sample (BAL) and not bronchial aspiration (or sputum). Others require 2 positive sputum cultures. Our results highlight the pressing need to implement non-invasive and validated diagnostic methods such as galactomannan antigen detection in this population [6,8]. Finally, the prognosis of aspergillosis is dramatically poor according to our study and published data. At the same time, the diagnosis of aspergillosis is dramatically poor according to detection in this population [6,8]. Finally, the prognosis of aspergillosis in critically ill patients without malignancy is difficult to achieve an efficient therapy. Patients on ECMO can have variability in antifungal pharmacokinetics, and this needs to be further studied [23].

Our study had several limitations. First, it was a retrospective study conducted at a single centre; further prospective studies are required to confirm our findings. Secondly, we used an algorithm not validated in this patient population – in particular, the sensitivity of BAL has been questioned [19]. Thirdly, because we did not practice systematic surveillance culture, our incidence may be an underestimate of the real incidence of Aspergillus in this population. Finally, it is also possible that Aspergillus may have been present prior to ICU admission but undiagnosed in some cases.

In conclusion, we found that Aspergillus may be a significant pathogen in patients requiring ECMO in terms of incidence and possibly of pathogenicity. Intensivists should be mindful of this potential risk and initiate antifungal treatment where indicated in this group of patients with a poor prognosis. Future studies should consider the feasibility and impact of more sensitive diagnostic strategies.

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References


Aspergillus in patients with ECMO support


