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Case Report

Survival After Invasive Pulmonary Aspergillosis in a Patient Requiring Sequential Veno-Arterial and Veno-Venous ECMO for Refractory Cardiorespiratory Failure: A Case Report

Edgar G. Moglia Ordaz*

Intensive Care Unit, Centro Médico Teknon, Quirónsalud, Barcelona, Spain.

***Corresponding Author:** Edgar G. Moglia Ordaz, Intensive Care Unit, Centro Médico Teknon, Carrer de Vilana, 12, 08022 Barcelona, Spain.

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Abstract

Background: Invasive Pulmonary Aspergillosis (IPA) in critically ill patients on Extracorporeal Membrane Oxygenation (ECMO) is a highly lethal condition, with mortality reported over 80%. Diagnosing and managing this condition is complicated by underlying severe illness, non-specific findings, and profound acquired immune dysfunction.

Case Presentation: We report the case of a 67-year-old female with no prior immunosuppression who survived a catastrophic 3-month ICU stay. She initially suffered a cardiac tamponade requiring surgical repair, which was complicated by a massive pulmonary embolism (PE) necessitating Veno-Arterial ECMO (VA-ECMO) and mechanical thrombectomy. After weaning from VA-ECMO, she developed severe ARDS from an *E. coli* ESBL pneumonia, requiring initiation of Veno-Venous ECMO (VV-ECMO). Because of persistent severe respiratory failure despite appropriate antibacterial treatment, bronchoscopy with bronchoalveolar lavage was performed. BAL galactomannan was positive at an optical density index of 0.7, whereas serum galactomannan and fungal cultures were negative. In the clinical context, this finding supported a working diagnosis of pulmonary aspergillosis and prompted the initiation of voriconazole. The diagnosis was subsequently strengthened by the isolation of *Aspergillus terreus* from a repeat BAL culture at the referral center. After 33 days, she was transferred to a referral center (Hospital Clínic), where VV-ECMO was weaned. However, she relapsed with severe respiratory failure. A new bronchoscopy confirmed invasive aspergillosis via culture of *Aspergillus terreus* and revealed high-load Cytomegalovirus (CMV) reactivation (240,000 copies/mL). She was successfully treated with a prolonged 7-week course of isavuconazole and ganciclovir. Her recovery was protracted, complicated by gastrointestinal bleeding and severe critical illness myopathy, but she was eventually weaned from all organ support and discharged to rehabilitation.

Conclusions: This case of survival highlights the extreme complexity of managing severe ARDS on ECMO. It underscores: The importance of proactive investigation for fungal and viral superinfections, such as *Aspergillus* and CMV, in patients with ARDS who fail to improve, as this indicates profound acquired immunoparalysis. The diagnostic utility of BAL galactomannan as an early marker, even when cultures are later positive for different species. That survival, while rare, is possible with aggressive, multidisciplinary management and prolonged antifungal therapy.

Keywords: *Case report; invasive pulmonary aspergillosis; extracorporeal membrane oxygenation; acute respiratory distress syndrome; Aspergillus terreus; galactomannan; cytomegalovirus reactivation; therapeutic drug monitoring.*

Background

Invasive Pulmonary Aspergillosis (IPA) has emerged as a significant threat in the intensive care unit (ICU), extending far beyond its classic association with severely immunocompromised hosts. Pulmonary aspergillosis is increasingly recognized in critically ill, non-neutropenic patients without classical immunosuppressive conditions. Severe acute respiratory distress syndrome, prolonged mechanical ventilation, broad-spectrum antimicrobial exposure, and extracorporeal membrane oxygenation may contribute to an increased risk of invasive fungal infection.[1]. Extracorporeal Membrane Oxygenation (ECMO), while a life-saving therapy for refractory cardiorespiratory failure, paradoxically increases the risk for IPA by inducing a state of systemic inflammation and immune dysregulation [2].

This constellation of ARDS, ECMO, and IPA is exceptionally lethal, with mortality rates consistently reported to exceed 80% [3]. The diagnosis is notoriously difficult, as clinical and radiological signs are non-specific. Furthermore, these patients often develop multiple concurrent infections, including viral reactivations such as Cytomegalovirus (CMV), which are markers of a profound acquired immunoparalysis and further complicate management [4].

We present the exceptional case of a 67-year-old female who survived this exact constellation: sequential VA-ECMO and VV-ECMO support, complicated by confirmed *Aspergillus terreus* pneumonia and high-load CMV reactivation. This report, which includes the full 3-month ICU course across two institutions, has been prepared in accordance with the CARE guidelines [5] and provides critical insights into the diagnostic and therapeutic challenges of this complex syndrome.

Case Presentation

Patient Information

A 67-year-old female with a history of hypertension, dyslipidemia, and atrial fibrillation (on Edoxaban) was admitted for an elective flutter ablation. She had no history of immunosuppression, neoplasia, or chronic lung disease.

Clinical Findings and Timeline

The patient's complex ICU course proceeded in distinct phases:

Phase 1: Cardiac Tamponade and Multicomponent Shock (Day 0-1)

On June 22nd, the ablation procedure was complicated by a laceration of the superior left pulmonary vein, leading to acute cardiac tamponade. Following an emergency pericardiocentesis (>700 mL) and surgical repair under cardiopulmonary bypass (CPB), she was transferred to the ICU. She presented in multi-component shock: vasoplegic (norepinephrine 0.8 mcg/kg/min), hemorrhagic (requiring >1000 mL blood loss replacement, 3 PRBCs, 1 platelet pool), and persistent hypoperfusion (Lactate > 4 mmol/L) with an echocardiogram showing a severely dilated right ventricle (RV).

Phase 2: VA-ECMO, PE Diagnosis, and the "First Hit" (Day 1-8)

A pulmonary artery catheter was placed, revealing obstructive shock (CI 1.85 L/min/m², mPAP 43 mmHg, PVRi 1082 dyn·s·cm^{-5}). Based on these findings, Veno-Arterial ECMO was initiated emergently on June 23rd. A subsequent angio-CT scan confirmed a massive "saddle" pulmonary embolism, which was treated with mechanical thrombectomy. The patient received significant transfusions during this period (>5 PRBCs, 3 platelet pools). Her RV function improved, and VA-ECMO was decannulated on June 29th. Notably, chest radiographs prior to decannulation already showed developing bilateral infiltrates.

Phase 3: The "Second Hit" and Refractory ARDS (Day 8-15)

On June 30th, 24 hours after weaning, she developed severe ARDS (PaO_2/FiO_2 < 100) and fever. A bronchial aspirate grew Escherichia coli ESBL. Despite Meropenem and prone positioning, her hypoxemia remained refractory, culminating in a cardiovascular collapse (desaturation to 30%) on July 6th. This necessitated urgent implantation of Veno-Venous ECMO.

Phase 4: IPA Diagnosis and Management (Day 15 onwards)

On VV-ECMO, the patient remained dependent on maximal support with persistent "white lung" imaging and poor lung compliance (<15 ml/cmH_2O). This failure to improve prompted a search for a secondary pathology.

Diagnostic Assessment

A bronchoscopy with bronchoalveolar lavage (BAL) was performed on July 7th.

- **Microbiology:** Bacterial and fungal cultures were negative.
- **Biomarkers:** Serum galactomannan was negative. BAL galactomannan was positive at an optical density index of 0.7, above the positivity threshold of 0.5 used by the local laboratory. Bacterial and fungal cultures from this initial BAL were negative. In the setting of persistent severe respiratory failure, diffuse pulmonary infiltrates, and failure to improve despite appropriate antibacterial therapy, the BAL galactomannan result supported a working diagnosis of pulmonary aspergillosis and prompted the initiation of antifungal treatment. However, because the patient lacked a classical EORTC/MSGERC host factor and the initial fungal culture was negative, this result was not considered definitive evidence of invasive disease.
- **Imaging:** A chest CT on July 18th showed diffuse bilateral infiltrates consistent with severe ARDS, but no classic nodules or halo signs.
- **Follow-up (at Referral Center):** After transfer, a relapse of respiratory failure prompted a new bronchoscopy. A repeat bronchoscopy performed at the referral center yielded *Aspergillus terreus* in BAL culture, substantially strengthening the diagnosis of pulmonary aspergillosis in the appropriate clinical and radiological context. Concurrently, BAL viral PCR revealed a high-load CMV reactivation (240,000 copies/mL).

Therapeutic Intervention

Treatment with voriconazole was started at our institution on July 11th. Due to a lack of clinical response, therapy was switched to isavuconazole on July 21st. Following the definitive diagnosis of *A. terreus* and CMV reactivation at the referral center, treatment with isavuconazole was continued for a total of 7 weeks, and ganciclovir was initiated.

Follow-up and Outcomes

After a 33-day ICU stay at our institution, the patient was transferred. At the referral center, she was weaned from VV-ECMO on August 2nd. Her recovery was protracted, complicated by a gastrointestinal bleed and severe critical illness myopathy. She was liberated from mechanical ventilation on September 1st and decannulated from her tracheostomy on October 1st. After a total of three months in two ICUs, she was discharged to a rehabilitation facility, hemodynamically stable and with good neurological condition, though with significant restrictive pulmonary sequelae.

Discussion

This case of survival from IPA on ECMO provides several critical learning points for intensivists.

The Diagnostic Challenge: Pulmonary Aspergillosis in a Critically Ill, Non-Neutropenic Patient

This case illustrates the diagnostic challenges of pulmonary aspergillosis in a critically ill, non-neutropenic patient without classical host factors for invasive fungal disease. The initial suspicion was rightly triggered by the "failure to improve" on ECMO, despite appropriate bacterial coverage. The BAL galactomannan index of 0.7 was an early microbiological finding that, when interpreted together with the absence of clinical improvement and the persistence of diffuse pulmonary infiltrates, supported the initiation of antifungal therapy. However, its limited specificity at this threshold and the negative initial fungal culture should be recognized. The subsequent isolation of *A. terreus* from BAL culture substantially increased the diagnostic likelihood of pulmonary aspergillosis.

The subsequent isolation of A. terreus and high-load CMV reactivation reveals the profound state of acquired immunoparalysis. The CMV reactivation itself is a known independent risk factor for mortality and secondary infections, including IPA [10]. The initial BAL GM positivity, followed by a culture for *A. terreus*, highlights the utility of GM as a broad early marker for *Aspergillus* invasion.

The "Three-Hit" Pathophysiology and Immune Paralysis

The patient's lung was subjected to a "first hit" (CPB, massive transfusion, TEP), followed by a "second hit" (*E. coli* VAP), leading to refractory ARDS. This sequence suggests a cumulative interaction among major surgery, cardiopulmonary bypass, massive transfusion, bacterial infection, severe ARDS, prolonged mechanical ventilation, and extracorporeal support. These exposures may have contributed to acquired immune dysfunction and susceptibility to secondary opportunistic infections. However, the proposed “three-hit” model remains an interpretative framework and cannot be demonstrated from this individual case [6]. The isolation of *A. terreus* is particularly noteworthy, as this species is known to be intrinsically resistant to Amphotericin B, making the azole-based therapy (isavuconazole) the correct choice [11].

The Therapeutic Conundrum: Pharmacokinetics on ECMO

The lack of response to voriconazole is a crucial teaching point. Azoles are lipophilic and are known to be sequestered by the ECMO circuit, leading to subtherapeutic drug levels in up to 60% of patients [7]. The switch to isavuconazole, a non-inferior alternative per the SECURE trial [8], was a logical step.

Self-Critical Analysis and Limitations

A critical review of our management reveals two potential areas for improvement, which serve as key limitations and learning points. First, the time to suspect IPA. While the initial focus on the *E. coli* VAP was appropriate, the failure to improve after 5-7 days of targeted antibiotic therapy could have, in retrospect, triggered an earlier search for fungal superinfection. Our pro-active bronchoscopy on day 8 of this phase (day 15 of initial ICU stay) was timely, but this case argues for including IPA in the differential diagnosis even earlier. Second, the absence of Therapeutic Drug Monitoring (TDM) for voriconazole represents a significant limitation. Given the well-documented pharmacokinetic variability on ECMO, relying on standard dosing may have contributed to the initial lack of clinical response. This case strongly supports the argument to incorporate TDM as a standard of care when using azoles in this population.

The diagnostic classification of pulmonary aspergillosis represents an additional limitation. The patient did not have a classical EORTC/MSGERC host factor, serum galactomannan was negative, and the initial BAL fungal culture was sterile. The initial BAL galactomannan index of 0.7 therefore supported clinical suspicion but could not independently establish invasive disease. The subsequent isolation of *A. terreus* strengthened the diagnosis, although histopathological confirmation was not obtained.

Survival Against the Odds

The survival of this patient starkly contrasts with the >80% mortality reported in the literature for IPA on ECMO [3]. The favorable outcome was likely multifactorial and may have been facilitated by the early characterization and treatment of obstructive shock, sequential extracorporeal support, repeated microbiological investigation, multidisciplinary care, and targeted antimicrobial therapy. However, the relative contribution of each intervention cannot be determined from a single case, and clinical improvement cannot be attributed exclusively to antifungal or antiviral treatment.

Conclusions

This case describes survival after a prolonged and complex critical illness requiring sequential VA-ECMO and VV-ECMO, complicated by pulmonary aspergillosis and high-load CMV reactivation. In critically ill patients with persistent or recurrent respiratory failure despite appropriate antibacterial therapy, repeated lower respiratory tract sampling and investigation for fungal and viral pathogens may be clinically informative.

A low-positive BAL galactomannan result should be interpreted cautiously and in conjunction with host characteristics, imaging findings, microbiological results, and clinical evolution. In this case, the subsequent isolation of *A. terreus* substantially strengthened the diagnosis of pulmonary aspergillosis.

ECMO and critical illness may alter antifungal pharmacokinetics, but inadequate voriconazole exposure could not be demonstrated because therapeutic drug monitoring was not performed. Therapeutic drug monitoring should be considered when voriconazole is used during ECMO, particularly when the clinical response is inadequate or substantial pharmacokinetic variability is anticipated.

Finally, the coexistence of *Aspergillus* infection and CMV reactivation was consistent with acquired immune dysfunction during prolonged critical illness, although immunoparalysis was not directly measured. This case supports a multidisciplinary and iterative diagnostic approach but does not establish causal relationships between individual interventions and the observed clinical outcome.

Declarations

The Institutional Ethics Committee of Centro Médico Teknon granted an exemption from requiring ethics approval for this case report.

Clinical Trial Number: Not applicable.

Consent for Publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of Data and Materials: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests: The author declare no competing interests.

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Authors' Contributions: E.G.M.O. was the primary physician involved in the patient's care, conceived of the case report, and drafted the manuscript

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