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Perfusion

# Venovenous extracorporeal life support in patients with HIV infection and *Pneumocystis jirovecii* pneumonia

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**Gerry Capatos,[1] Christopher R. Burke,[2] Mark T. Ogino,[3] Roberto R. Lorusso,[4] Thomas V. Brogan,[5] D. Michael McMullan[2] and Heidi J. Dalton[6]**

**Abstract**

*Aim:* As experience with extracorporeal life support (ECLS) increases, indications for its use have expanded to diverse patient populations, including those with HIV infection. *Pneumocystis jirovecii* pneumonia (PJP) is a particularly devastating complication of HIV infections. The objective of this study was to review ECLS use in HIV-positive patients, with particular emphasis on those with concomitant PJP infection.

*Methods:* All patients were treated by the same ECLS team, consisting of an ECLS specialist intensivist, cardiothoracic surgeon and allied medical professionals at three healthcare institutions. The same ECLS protocol was utilized for all patients during the study period. A retrospective review was performed for all HIV-positive patients placed on ECLS from May 2011 to October 2014. Demographic, clinical, ECLS and complication data were reviewed to identify risk factors for death.

*Results:* A total of 22 HIV-positive patients received ECLS therapy during the study period. All patients were supported with venovenous ECLS and overall survival to hospital discharge was 68%. Survival amongst the PJP positive cohort was 60%. Non-survivors were more likely to require inotropic medications on ECLS (100% non-survivors vs. 46.7% survivors, p=0.022) and had a longer total duration of ECLS (13 days non-survivors vs. 7 days survivors, p=0.011). No difference was observed between PJP-positive and PJP-negative patients with regard to demographic data, complication rates or survival.

*Conclusion:* ECLS is a viable treatment option in carefully selected HIV-positive patients, including those with severe disease as manifested by PJP infection.

## Introduction

Extracorporeal life support (ECLS) use for adult respiratory failure has increased dramatically in the years following the CESAR trial, which was published in 2009 and demonstrated the efficacy of this lifesaving therapy in adult patients with severe respiratory failure.[1,2] Improvements in technology and increased provider experience have resulted in the safer delivery of this therapy to an increasingly diverse patient population. Despite severe immunodeficiency and chronic, life-limiting illnesses traditionally being considered contraindications for ECLS, case reports of its use in human immunodeficiency virus (HIV)-infected patients have recently been published.[3]

*Pneumocystis jirovecii* pneumonia (PJP) is a particularly devastating complication of HIV infection, with mortality rates as high as 43% when mechanical ventilation is required.[4] Several case reports have recently reported the use of ECLS in HIV-positive patients with respiratory failure secondary to PJP infection.[5-7] Initial results in these patients are promising and, combined

[1]Arwyp Medical and ECMO Centre, Johannesburg, South Africa
[2]Division of Cardiac Surgery, Seattle Children's Hospital, Seattle, Washington, USA
[3]Division of Neonatology, Nemours/Alfred I. DuPont Hospital for Children, Wilmington, Delaware, USA
[4]Department of Cardiothoracic Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands
[5]Division of Critical Care Medicine, Seattle Children's Hospital, Seattle, Washington, USA
[6]INOVA Fairfax Medical Center, Fairfax, Virginia, USA

**Corresponding author:**
Heidi J. Dalton, INOVA Fairfax Medical Center, 3300 Gallows Rd, Falls Church, VA 22042
Email: Heidi.dalton26@gmail.com

with data suggesting that HIV patients treated with antiretroviral therapy (ART) may have a normal life expectancy,[8] enthusiasm for ECLS use in HIV patients continues to grow.

This study was conducted at three private care facilities in South Africa where a single ECLS team cared for HIV-positive patients using the same protocol. The goal of the present study was to retrospectively review the results of ECLS use in HIV patients and compare the results when concomitant PJP infection was present.

## Methods

This study protocol was approved by the local institutional review board and a waiver of consent was obtained. An internal database was reviewed to identify all patients with confirmed HIV infection who received ECLS from May 2011 to October 2014. All patients received extracorporeal life support via venovenous cannulation. In this mode, blood is both drained and reinfused into the patient's venous circulation. Adequate cardiac function must be maintained for this mode of extracorporeal membrane oxygenation (ECMO) support to provide systemic support. Demographic and clinical data, including HIV-specific indices (HIV viral load, CD4 counts) and outcome data was collected for all patients. ECLS-specific complication data was collected and grouped into specific categories: 1) mechanical complications, including circuit thrombosis, oxygenator failure or cannula malfunction; 2) hemorrhage (cannula site, pulmonary or gastrointestinal); 3) renal failure (Cr>1.5 or need for renal replacement therapy); 4) bacteremia/sepsis confirmed by culture data; and 5) cardiac dysfunction, defined as the requirement of inotropes while on ECLS. Patients were then stratified by the presence of confirmed PJP infection during the time of ECLS and outcomes were compared to those without PJP.

Data are reported as percentages for categorical variables and median with interquartile range (IQR) for continuous variables. The primary outcome measure was survival to hospital discharge. Categorical variables were analyzed with the Chi-square or Fisher's exact test while non-normally distributed data were analyzed using the Mann-Whitney test or the Kruskal-Wallis test. Stata SE 12 software (Stata Inc., College Park, TX, USA) was used for analysis. The authors had full access to the data and take responsibility for its integrity.

## Results

A total of 22 patients were identified and included in the final analysis. Fifteen (68%) patients survived to hospital discharge. All patients were supported with venovenous ECLS. A comparison of hospital survivors and non-survivors is shown in Table 1. Demographic, HIV viral load, CD4 cell count and rates of antiretroviral therapy (ART) did not differ between the two groups. Rates of PJP infection were similar between the survivors and non-survivors. Non-survivors had a longer total ECLS duration (13 days non-survivors vs. 7 days survivors, p=0.011) and a higher rate of inotrope usage on ECLS (100% non-survivors vs. 46.7% survivors, p=0.022). All remaining complications were similar between the two groups.

The patients were then stratified according to PJP infection status (Table 2). A total of 15 (68%) had respiratory failure secondary to PJP infection prior to initiation of ECLS. Overall survival in this group was 60% compared to 85.7% in the PJP negative group (p=0.35). PJP-positive patients had a lower CD4 cell count on admission compared to PJP negative patients (19.5 PJP positive vs. 78 PJP negative, p=0.039). All remaining demographic, clinical and complication data were similar between the two groups.

## Discussion

Extracorporeal life support has become an essential adjunctive therapy in the management of patients with severe cardiopulmonary failure. ECLS use in adult patients has only recently become widespread and adults now represent the fastest growing patient population.[1] Previously, chronic life-limiting illness has been considered a relative contraindication for ECLS use. As experience with this therapy has increased, indications have expanded into novel populations, including patients with HIV infection. Several case reports of ECLS use in HIV-positive patients have been published with promising results, including those with severe opportunistic infections, such as PJP.[3,5-7] Furthermore, the recognition that HIV-positive patients receiving antiretroviral therapy may experience a normal life expectancy[8] has increased enthusiasm amongst the ECLS community to consider these patients as viable candidates for extracorporeal support.

This is a 3 center study of patients cared for by a single ECMO. A majority (68%) of patients in this series had confirmed PJP infection prior to placement on extracorporeal support. All patients in this series presented with respiratory failure and received venovenous support. The results are promising, with an overall survival of 68%. In the cohort of patients with concomitant PJP infection, survival was 60% and did not differ significantly from the PJP-negative cohort.

The management of the HIV patient with PJP superinfection remains a formidable challenge. PJP infection often progresses rapidly in HIV patients and, when severe, results in substantial mortality.[4] PJP infection

**Table 1.** Demographics, HIV indices, clinical data and complications according to hospital survival.

| | Survivors (n=15) | Non-survivors (n=7) | Total (n=22) | p-value |
|---|---|---|---|---|
| **Age (years)** | 35 (33-52) | 42 (32-47) | 38.5 (33-50) | 0.916 |
| **Gender (% male)** | 7 (46.7%) | 3 (42.9%) | 10 (45.5%) | 1 |
| **Admission CD4 count (cells, $mm^3$)** | 63.5 (9-97) | 21 (15-37) | 41 (12-89) | 0.509 |
| **HIV viral load** | 174288 (4869-557914) | 503842 (97619-970486) | 190574 (95733-601147) | 0.316 |
| **ART pre-ECLS** | 13 (86.7%) | 7 (100%) | 20 (90.9%) | 1 |
| **PJP positive** | 9 (60%) | 6 (85.7%) | 15 (68.2%) | 0.35 |
| **Lowest pH pre-ECLS** | 7.36 (7.26-7.42) | 7.30 (7.23-7.48) | 7.33 (7.26-7.42) | 0.805 |
| **Highest lactate pre-ECLS (mg/dL)** | 2.0 (0.9-2.9) | 2.9 (2.7-3.6) | 2.1 (1.1-4.4) | 0.259 |
| **Lowest $PaO_2$ pre-ECLS (mmHg)** | 49 (45-73) | 76 (42-88) | 53 (45-79) | 0.307 |
| **Highest $PCO_2$ pre-ECLS (mmHg)** | 46 (35-52) | 40 (28-64) | 45 (33-52) | 0.647 |
| **Lowest P:F ratio pre-ECLS** | 76 (49-146) | 82 (56-126) | 79 (52-126) | 0.86 |
| **Murray score pre-ECLS** | 3.25 (3-3.5) | 3.5 (3.25-3.5) | 3.25 (3-3.5) | 0.167 |
| **Lowest SBP pre-ECLS (mmHg)** | 99 (89-119) | 119 (114-128) | 104 (91-120) | 0.119 |
| **Inotropes pre-ECLS** | 4 (28.6%) | 0 | 4 (22.2%) | 0.524 |
| **Albumin pre-ECLS (g/L)** | 24 (20-27) | 23.5 (19-26.5) | 24 (20-27) | 0.802 |
| **ECLS duration (days)** | 7 (6-11) | 13 (12-15) | 9.5 (7-13) | 0.011 |
| **24-hour ECLS flow (L/min)** | 3.2 (2.1-3.8) | 2.9 (2.7-3.6) | 3.1 (2.6-3.8) | 0.861 |
| **Mechanical complications** | 1 (6.7%) | 1 (14.3%) | 2 (9.1%) | 1 |
| **Bleeding** | 8 (53.3%) | 4 (57.1%) | 12 (54.6%) | 1 |
| **Renal failure** | 6 (40%) | 2 (28.6%) | 8 (36.4%) | 1 |
| **Dialysis** | 3 (20%) | 2 (28.6%) | 5 (22.7%) | 1 |
| **Bacteremia/Sepsis** | 7 (46.7%) | 4 (57.1%) | 11 (50%) | 1 |
| **Inotropes on ECLS** | 7 (46.7%) | 7 (100%) | 14 (63.6%) | 0.022 |

ART: antiretroviral therapy; PJP: Pneumocystis jirovecii; SBP: systolic blood pressure

can result in significant lung fibrosis that contributes, at least in part, to the substantial mortality seen in patients with severe disease.[9] A critical component of caring for these patients is early recognition and diagnosis and initiation of treatment, as delayed diagnosis of PJP infection has been found to be independently associated with increased mortality.[10,11] The ECLS team's approach to the patients' in this study consisted of the following: HIV-positive patients suspected of having PJP are aggressively screened by means of tracheal aspirate, LDH testing and (13)-beta-D-glucan testing.[12,13] Once PJP is diagnosed, appropriate antimicrobial and supportive care is immediately instituted, including ART and corticosteroids. PJP infected patients requiring prolonged periods of mechanical ventilation have previously been shown to have increased the odds of mortality.[14] Therefore, we have adopted a strategy of early ECLS initiation in these patients. Patients are given a non-invasive ventilation trial and, if failure occurs, they are placed on ECLS within 24 hours of the initiation of mechanical ventilation. If multi-system organ failure is present early in the disease course, patients are not offered extracorporeal support.

Once ECLS is commenced, patients are transitioned to an ultra-lung protective ventilation strategy, with minimization of airway pressures and tidal volumes. Sedation is rapidly weaned to allow the patient to be awake, but comfortable. ECLS sweep flow is adjusted to minimize respiratory drive and once patients are comfortable and able to maintain a normal respiratory rate, they are switched to continuous positive airway pressure (CPAP), with minimal settings. Extubation is typically attempted thereafter, thus, facilitating interaction with family and staff as well as mobilization. Enteral nutrition is instituted early and extubated patients are supplemented with nutritional drinks. ECLS and clinical parameters are continuously assessed to determine the optimal timing for weaning from extracorporeal support. Patients are removed from extracorporeal support as soon as they show signs of pulmonary improvement and are deemed safe to liberate from ECLS.

This study has several important limitations. It is retrospective in nature and subject to all selection and reporting biases inherent in retrospective studies. It is also a single-center report and center-specific practice patterns may be present that could render the results not

**Table 2.** Demographics, HIV indices, clinical data and complications according to Pneumocystis jirovecii infection status.

| | PJP positive (n=15) | PJP negative (n=7) | p-value |
|---|---|---|---|
| **Age (years)** | 39 (33-50) | 35 (34-52) | 0.832 |
| **Gender (% male)** | 5 (33.3%) | 5 (71.4%) | 0.172 |
| **Admission CD4 count (cells/mm$^3$)** | 19.5 (7-65) | 78 (62-111) | 0.039 |
| **HIV viral load** | 190574 (95733-601147) | 198428 (8624-1000007) | 0.763 |
| **ART pre-ECLS** | 14 (93.3%) | 6 (85.7%) | 1 |
| **Highest lactate pre-ECLS (mg/dL)** | 2.5 (1.3-4.5) | 1.6 (0.7-2.2) | 0.169 |
| **Lowest pH pre-ECLS** | 7.30 (7.28-7.47) | 7.36 (7.23-7.42) | 0.805 |
| **Lowest $PaO_2$ pre-ECLS (mmHg)** | 54.7 (41-82) | 46.1 (45-79) | 0.944 |
| **Highest $PCO_2$ pre-ECLS (mmHg)** | 39.5 (29.6-52) | 46.6 (39-64.1) | 0.245 |
| **Lowest P:F ratio pre-ECLS** | 82 (52-126) | 76 (46-458) | 0.86 |
| **Murray score pre-ECLS** | 3.38 (3.13-3.5) | 3.25 (3-3.5) | 0.54 |
| **Lowest SBP pre-ECLS (mmHg)** | 100 (91-115) | 120 (79-132) | 0.351 |
| **Inotropes pre-ECLS** | 2 (15.4%) | 2 (40%) | 0.533 |
| **Albumin pre-ECLS (g/L)** | 24.5 (21-26) | 22 (19-28) | 0.899 |
| **ECLS duration (days)** | 12 (8-15) | 7 (6-9) | 0.066 |
| **24 hour ECLS flow (L/min)** | 3.3 (2.7-3.7) | 3 (2.1-4.4) | 0.634 |
| **Mechanical complications** | 2 (13.3%) | 0 | 1 |
| **Bleeding** | 10 (66.7%) | 2 (28.6%) | 0.172 |
| **Renal failure** | 5 (33.3%) | 3 (42.9%) | 1 |
| **Dialysis** | 2 (13.3%) | 3 (42.9%) | 0.274 |
| **Bacteremia/Sepsis** | 8 (53.3%) | 3 (42.9%) | 1 |
| **Inotropes on ECLS** | 11 (73.3%) | 3 (42.9%) | 0.343 |
| **Survival** | 9 (60%) | 6 (85.7%) | 0.35 |

ART: antiretroviral therapy; PJP: Pneumocystis jirovecii; SBP: systolic blood pressure

generalizable to the entire ECLS community. Finally, although it is the largest series to date on ECLS use in HIV-positive patients, the results must be taken in the context of the limited sample size present. Despite these limitations, this report provides evidence that, in HIV-positive patients presenting with respiratory failure (including those with concomitant PJP infection), a strategy of early ECLS initiation, aggressive extubation and early mobilization/nutritional support can lead to promising results, with minimal complication rates and survival to hospital discharge exceeding 60%.

## Conclusion

The treatment of HIV-positive patients complicated by PJP pneumonia remains a challenge, with significant mortality associated with medical care alone. We present the largest case series to date of HIV-positive patients with severe respiratory failure supported with ECLS, of which fifteen patients had concomitant PJP infection. By utilizing a strategy of prompt PJP identification and treatment, early institution of ECLS and aggressive mobilization on ECLS, we have been able to obtain optimal outcomes in these challenging patients. Continued study in ECLS use in this novel patient population will allow further identification of factors associated with optimal outcomes.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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