Surviving White-out: How to Manage Severe Noninfectious Acute Lung Allograft Dysfunction of Unknown Etiology

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INTRODUCTION

Acute respiratory failure is the leading cause for intensive care unit (ICU) readmission in lung transplant recipients and is associated with high mortality; 25% of patients the etiology is unknown.1-3 Successful management of severe noninfectious acute lung allograft dysfunction (ALAD) is poorly described. Moreover, there may be reluctance to augment immunosuppression for this proinflammatory condition in the ICU setting because of potential infectious complications.4,5 A pragmatic, evidence-based approach to managing this population is needed.

We report the successful management of 5 lung transplant recipients with severe noninfectious ALAD of unknown etiology who were supported with extracorporeal membrane oxygenation (ECMO) within 48h of respiratory failure. We also utilized anti-inflammatory therapies, including steroids, plasma exchange (PLEX), intravenous immunoglobulin (IVIg), antithymocyte globulin, and alemtuzumab.

We demonstrate that with aggressive care, severe noninfectious ALAD is a survivable condition.

MATERIALS AND METHODS

Study Design, Setting, and Participants

We reviewed all lung transplant recipients admitted to the ICU between January 1, 2018, and September 1, 2021. Patients were diagnosed with severe ALAD of unknown etiology if they met the following: (1) single or bilateral lung transplant; (2) discharge from the index hospitalization; (3) readmission with acute (<7 d) respiratory failure with diffuse allograft opacification on imaging with partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) < 200 mm Hg; and (4) without concurrent extrapulmonary failure at presentation.3,4 Patients were excluded if there was an identifiable etiology to their respiratory failure. Infection was excluded if sputum, tracheal aspirates, or bronchoalveolar lavage fluid (BALF) cultures were negative or if antigen or antibody testing of body fluids was negative.7 Cell count, microbial cultures, viral polymerase chain reaction, and 1,3-BD glucan and galactomannan were obtained on BALF. Antibody-mediated rejection was excluded if patients failed to meet International Society for Heart and Lung Transplantation consensus criteria for possible, probable, or definite disease (depending on the availability of histology).3,4 When tissue was unobtainable, acute cellular rejection was excluded by a lack of improvement within 3 d of high-dose steroid administration.9,10 All patients were treated with standard maintenance immunosuppression (calcineurin inhibitor, antiproliferative, and prednisone).11 This study was approved by the Vanderbilt University Medical Center (VUMC) Institutional Review Board (No. 201951).

Medical Management for Severe Noninfectious ALAD

We initiated venovenous ECMO (VV-ECMO) support within 48h for patients with respiratory failure refractory to high-flow nasal cannula to minimize ventilator-associated lung injury, sedation, and deconditioning. Criteria for ECMO included: PaO2/FiO2 <200 or pH < 7.25 due to a primary respiratory acidosis.12 A bicaval dual-lumen cannula was inserted to maximize mobility. ECMO settings were adjusted to maintain arterial oxygen saturation > 90% and pH between 7.35 and 7.45.13 Patients were anticoagulated with unfractionated heparin (goal-activated partial thromboplastin time of 40–60 s).14

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Patients were sedated for a goal Richmond Agitation and Sedation Score 0 to −2. Vent settings were adjusted to target plateau pressures <25 cm H₂O, positive end-expiratory pressure 10–15 cm H₂O, and respiratory rate <10 breaths/min. When possible, patients were liberated from mechanical ventilation. Early tracheostomy was performed in patients unable to tolerate extubation.

Patients with severe ALAD received antimicrobials for multidrug-resistant organisms with Vancomycin, an anti-pseudomonal extended-spectrum penicillin or beta-lactam, and therapy for intracellular bacteria. Broader therapy was provided based on colonization history. Antimicrobials were de-escalated after 48 h, when appropriate. Once infection was excluded, patients were administered methylprednisolone 10–15 mg/kg daily × 3.

If there was no response, patients received PLEX × 5 sessions (1.5 × plasma volume), IVIg, ± rituximab. If there was a lack of improvement and patients still required invasive mechanical ventilation with FiO₂ >40% after 3 d, we added antithymocyte globulin or alemtuzumab based on clinician preference.

**Outcomes**

The primary outcome was forced expiratory volume in 1 s (FEV1) following hospital discharge. Spirometry was performed in the VUMC pulmonary function testing laboratory according to the American Thoracic Society criteria. Secondary outcomes included survival, length of stay (LOS), change in sequential organ failure assessment scores and incidence of de novo donor-specific antibodies (dnDSA).

**TABLE 1.**

| Patients baseline characteristics | No. 1 | No. 2 | No. 3 | No. 4 | No. 5 | N (%) or median (IQR) |
|----------------------------------|-------|-------|-------|-------|-------|-----------------------|
| **Baseline traits**              |       |       |       |       |       |                       |
| Native interstitial lung disease | No    | Yes   | Yes   | Yes   | No    | 3 (60%)               |
| Bilateral lung transplant        | Yes   | Yes   | Yes   | No    | No    | 2 (40%)               |
| Age at time of ALAD (y)          | 31    | 65    | 59    | 67    | 71    | 65 (59–67)            |
| Male gender                      | No    | Yes   | Yes   | Yes   | Yes   | 4 (80%)               |
| Cytomegalovirus D+/R− status     | Yes   | No    | No    | No    | No    | 1 (20%)               |
| Lung allocation score            | 37.36 | 49.94 | 52.02 | 34.35 | 32.44 | 37.36 (34.35–49.94)   |
| Donor ischemic time (min)        | 356   | 311   | 241   | 347   | 257   | 311 (257–347)         |
| Posttransplant HLA crossmatch    | Negative | Negative | Negative | Negative | Negative | 100%                  |
| PGD score 72 h                   | 1     | 1     | 1     | 1     | 1     | 3 (1–1)               |
| Gastroesophageal reflux disease  | No    | No    | Yes   | No    | Yes   | 2 (40%)               |
| **Pre-ALAD pulmonary function**  |       |       |       |       |       |                       |
| Baseline FEV1 (L)                | 1.78  | 4.6   | 1.56  | 2.4   | 1.47  | 1.78 (1.56–2.40)      |
| Baseline FEV1, % predicted       | 59    | 117   | 43    | 81    | 52    | 59 (52–80)            |
| Last FEV1 before ALAD (L)        | 1.51  | 4.56  | 1.56  | 2.34  | 1.44  | 1.56 (1.51–2.34)      |
| Last FEV1 before ALAD, % predicted| 50    | 116   | 43    | 79    | 52    | 52 (50–79)            |
| **Severe ALAD characteristics**  |       |       |       |       |       |                       |
| ALAD onset posttransplant (d)    | 72    | 39    | 28    | 345   | 311   | 72 (39–311)           |
| Chest imaging (at ECMO cannulation) |       |       |       |       |       |                       |
| Reticulonodular opacities        | Yes   | Yes   | Yes   | Yes   | Yes   | 5 (100%)              |
| Ground glass opacities           | Yes   | Yes   | Yes   | Yes   | Yes   | 5 (100%)              |
| Consolidation                    | Yes   | Yes   | Yes   | Yes   | Yes   | 5 (100%)              |
| Diffuse opacification            | Yes   | Yes   | Yes   | Yes   | Yes   | 5 (100%)              |
| Pleural thickening/effusions     | No    | No    | Yes   | Yes   | Yes   | 3 (60%)               |
| **Mechanical ventilation at ECMO cannulation** |       |       |       |       |       |                       |
| Plateau pressure                 | N/A   | 40    | 30    | 36    | 25    | 33 (29–37)            |
| Driving pressure                 | N/A   | 28    | 20    | 22    | 20    | 21 (20–24)            |
| Positive end-expiratory pressure | N/A   | 12    | 10    | 14    | 5     | 11 (9–13)             |
| PaO₂/FiO₂ at ECMO cannulation    | 96    | 61    | 137   | 108   | 79    | 96 (79–108)           |
| DSA                              | 0     | 0.07 (MR = 3061) | 0 | 0 | 0 | 1 (20%) |
| **Bronchoalveolar lavage traits** |       |       |       |       |       |                       |
| Total cells                      | 500   | 250   | 186   | 435   | 233   | 250 (233–435)         |
| Percent neutrophils              | 59    | 29    | 9     | 85    | 68    | 59 (29–68)            |
| Percent lymphocytes              | 17    | 33    | 7     | 0     | 20    | 17 (7–20)             |
| Percent eosinophils              | 4     | 3     | 6     | 0     | 1     | 3 (1–4)               |
| Percent monocytes                | 20    | 35    | 78    | 15    | 11    | 20 (15–35)            |

ALAD, acute lung allograft dysfunction; D, donor; DSA, donor-specific antibodies; ECMO, extracorporeal membrane oxygenation; FEV1, forced vital capacity in 1 s; FiO₂, fraction of inspired oxygen; IQR, interquartile range; MR, mean fluorescence intensity; PaO₂, partial pressure of oxygen; PGD, primary graft dysfunction; R, recipient.
**Statistical Analyses**

Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as numbers and percentages. A P value <0.05 was significant. We compared continuous variables using a Wilcoxon signed-rank sum test. Statistical analyses were performed using STATA17 (College Station, TX).

**RESULTS**

**Demographics**

During the study period 95 lung allograft recipients were admitted to an ICU at VUMC following their index hospitalization, 6 of whom met criteria for severe noninfectious ALAD (see Table 1). Imaging showed “white-out” with diffuse reticulonodular opacities in the affected allografts for all patients. One patient was excluded because of early (<24h) goals of care limitations. The remaining 5 patients received VV-ECMO and immunomodulation. Baseline demographics and pre-ECMO lung function are detailed (Table 1).

**Diagnostics**

All patients underwent bronchoscopy to exclude infection. BALF was hypercellular in all cases; median cell count was 250/µL (IQR 233–435) and was neutrophilic (median 59%, IQR 29%–68%). DSA assessment was negative in 4 cases. Patient 2 had dnDSA, though surgical lung biopsy pathology did not show capillaritis, neutrophilic demargination, or C4d staining.

**Management**

All patients received antibiotics and corticosteroids. Four patients received PLEX × 5 sessions and IVIg (0.5–2 g/kg). Three patients received lymphocyte-depleting therapies (Table 2). ECMO was initiated a median 4 d postadmission (IQR 1–4). Four patients were liberated from mechanical ventilation on ECMO; delirium precluded extubating the fifth. Duration of ECMO was 21 d (IQR 7–28) (see Table 2).

**Outcomes**

Median ICU and hospital LOS were 31 d (IQR 13–33) and 42 d (IQR 21–47), respectively. All patients survived to hospital discharge and 60 d following ECMO decannulation. Two patients were discharged home, and the remainder were discharged to inpatient rehabilitation. Three patients developed infections following treatment with lymphocyte-depleting therapies; 2 patients had pseudomonal pneumonia with 1 having concomitant *Clostridium difficile*. The third patient developed a *Mycobacterium avium* pleuritis. There was a ~50% reduction in sequential organ failure assessment scores with treatment [median 9 (IQR 7–11) versus 5 (IQR 4–6), respectively, P = 0.06; see Table 3].

FEV1 >30 d after hospital discharge was decreased in 3 patients, although the patient with the greatest decline had significant improvement over time (Figure 1). The last recorded median FEV1 for the entire cohort was 52% predicted, similar to baseline values (59%, IQR 52–80, P = 0.06) (Table 3; Figure 1). At the end of the study period, 4 patients were alive with intact allograft function, not requiring supplemental oxygen, and independent of activities of daily living. The patient that died developed allograft failure due to nonadherence with immunosuppression. None of the patients in this series developed dnDSA. Median follow-up was 442 d (IQR 120–493).

**DISCUSSION**

Severe noninfectious ALAD is associated with high rates of allograft failure; effective management strategies are not well-described.3,21,22 We show that early, aggressive management with VV-ECMO and augmented immunosuppression leads to acceptable outcomes. Based on our experience, we provide

**TABLE 2.** Summary of advanced management

| Therapy                                      | Patient   | No. 1 | No. 2 | No. 3 | No. 4 | No. 5 | N (%) or median (IQR) |
|----------------------------------------------|-----------|-------|-------|-------|-------|-------|-----------------------|
| VV-ECMO management                           | Time from hospital admission to ECMO start (d) | 1 4   | 8     | 0     | 4     | 4   | 4 (1–4)               |
|                                              | Mechanical ventilation days on ECMO | 0 0   | 0     | 23    | 0     | 0   | 0                      |
| VV-ECMO configuration                        | 28Fr DL 30Fr DL 30Fr DL 30Fr DL 30Fr DL | R. Uv R. Uv R. Uv R. Uv R. Uv | ---   | 3.36  | 5.3   | 4.9 | 4.3                   |
|                                              | Estimated cardiac output (L/min) | 3.36  | 5.3   | 4.9   | 4.3   | 4.3 | 4.3 (4.3–4.9)         |
|                                              | Max blood flow (L/min) | 3     | 4.9   | 4.95  | 4.48  | 4.22| 4.48 (4.22–4.9)       |
|                                              | Max sweep gas flow (L/min) | 7     | 6     | 8.5   | 8     | 3   | 7 (6–8)               |
|                                              | Tracheostomy on ECMO | No    | Yes   | No    | Yes   | No   | 2 (20%)               |
| Augmented immunosuppression                  | Plasmapheresis | Yes   | Yes   | Yes   | Yes   | Yes | No 4 (80%)            |
|                                              | Intravenous immunoglobulin | Yes   | Yes   | Yes   | Yes   | Yes | No 4 (80%)            |
|                                              | Rituximab | No    | Yes   | No    | No    | No   | 1 (20%)               |
|                                              | Antithymocyte globulin | Yes   | No    | No    | Yes   | Yes | 3 (60%)               |
|                                              | Alemtuzumab (campath) | Yes   | No    | No    | No    | No   | 1 (20%)               |
|                                              | PT | | | | | | |
|                                              | PT sessions on ECMO | 2 4   | 1     | 0     | 2     | 2   | 2 (1–2)               |

*Estimated cardiac output = 2.4 x body surface area.
*Ambulated daily with nursing, in addition to dedicated physical therapy sessions.
*IQR, interquartile range; PT, physical therapy; VV-ECMO, venovenous extracorporeal membrane oxygenation.
a framework for clinicians managing this serious condition (Figure 2).

We believe that the favorable outcomes may be due to early utilization of ECMO support. The proactive use of ECMO obviated the need for positive pressure ventilation, which is harmful to injured lungs.23 Furthermore, early ambulatory ECMO reduces the need for sedation, allows for physical therapy, reduces delirium, and improves ICU and hospital LOS.15 Additionally, our approach relies on timely augmentation of immunosuppression. Two patients improved after receiving antibody-mediated rejection-directed therapies despite absence of DSA; it is possible that inflammation was mediated by non–donor-specific HLA antibodies. Prior work established a role for autoantibodies in ALAD pathogenesis.24 We also utilized lymphocyte-depleting therapies when necessary. Although these therapies are commonly used in the ambulatory setting, there are few reports describing their use in critically ill patients. Clinicians may be wary to

### TABLE 3. Outcomes

| Patient | No. 1 | No. 2 | No. 3 | No. 4 | No. 5 | N (%) or median (IQR) |
|---------|-------|-------|-------|-------|-------|-----------------------|
| Days on ECMO | 29 | 21 | 4 | 28 | 7 | 21 (7–28) |
| Survival to hospital discharge | Yes | Yes | Yes | Yes | Yes | 5 (100%) |
| 60-d survival after ECMO cannulation | Yes | Yes | Yes | Yes | Yes | 5 (100%) |
| 60-d occurrence of superinfection | Yes | Yes | No | No | No | 2 (50%) |
| SOFA score at ECMO cannulation | 2 | 6 | 7 | 5 | 4 | 5 (4–6) |
| SOFA score at ECMO decannulation | 2 | 11 | 11 | 9 | 7 | 9 (7–11) |
| ICU LOS (d) | 41 | 31 | 13 | 33 | 12 | 31 (13–33) |
| Hospital LOS (d) | 47 | 61 | 21 | 46 | 14 | 46 (21–47) |
| Disposition to home at hospital discharge | Yes | No | No | No | Yes | 2 (40%) |
| FEV1 pre-ALAD (L) | 1.51 | 4.56 | 1.56 | 2.34 | 1.44 | 1.56 (1.51–2.34) |
| FEV1 pre-ALAD, % predicted | 50 | 116 | 43 | 79 | 52 | 52 (50–79) |
| FEV1 1-mo post-ALAD (L) | 1.37 | 1.91 | 2.30 | 1.81 | 1.32 | 1.81 (1.37–1.91) |
| FEV1 1-mo post-ALAD (% predicted) | 46 | 48 | 63 | 61 | 48 | 48 (48–61) |
| De novo donor-specific HLA antibodies within 6 mo of severe ALAD? | No | No | No | No | No | 0 |

ALAD, acute lung allograft dysfunction; ECMO, extracorporeal membrane oxygenation; FEV1, forced vital capacity in 1 s; IQR, interquartile range; LOS, length of stay; SOFA, sequential organ failure assessment.

![FIGURE 1.](image) The trend in FEV1 (L) in patients post-ALAD of unknown etiology. Trend in FEV1 over time prior to and following the episode of ALAD. The first patient died several weeks after her ALAD event. All other patients FEV1 trend is depicted for values that are available up to 12 mo post-ALAD event. ALAD, acute lung allograft dysfunction; FEV1, forced vital capacity in 1 s.
Management Considerations:

+ High flow nasal cannula (HFNC) to keep SpO2 >90%
+ Avoid positive-pressure ventilation
+ Peripheral Venovenous Extracorporeal Membrane Oxygenation (ECMO) support to support gas-exchange if
  - pH < 7.25 due to a primary respiratory acidosis
  - PaO2 / FiO2 < 150 with SpO2 <90% for >3 hours despite HFNC
  - Suggest cannulation strategy that supports physical therapy
  - Suggest cannulation strategy where blood flow > 60% of cardiac output
+ If patient is intubated to facilitate ECMO cannulation, consider early extubation
+ Minimize/ avoid sedation

Diagnosis Algorithm:

+ Bronchoscopy with bronchoalveolar lavage
  - Include cell count / differential, bacterial and fungal cultures/stains, viral Polymerase chain reaction (PCR)
+ Computed-tomography Chest
+ Blood fungal markers
+ Cytomegalovirus PCR
+ Seasonal / geographic- appropriate parasite evaluation
+ Consider tissue diagnosis with transbronchial biopsy or surgical lung biopsy

Treatment Considerations:

+ Empiric broad-spectrum antibiotics; de-escalate if culture negative after 48-72h
+ Pulse corticosteroids (Methylprednisolone 7.5- 15mg/kg daily x 3 days)

If no clinical improvement:

+ Empiric treatment for Antibody Mediated Rejection
  - Plasmapheresis x 5 treatments
  - Intravenous Immunoglobulin (2g/kg, divided in two daily doses)
  - Consider Rituximab if not using lymphocyte-depleting therapies
+ Empiric lymphocyte-depleting therapies
  - Rabbit-Antithymocyte globulin (5-7mg/kg total dose, as tolerated)
  - Alemtuzumab 30mg x once (Subcutaneous or Intravenous)

FIGURE 2. Recommended management strategy for patients with severe, noninfectious ALAD. We provide a proposed strategy for management of patients with severe ALAD, including advice on diagnosis, support, and treatment. ALAD, acute lung allograft dysfunction; PaO2, partial pressure of oxygen; SpO2, saturation of peripheral oxygen.

augment immunosuppression in the ICU because of infection risk, so we posit that aggressive therapy is necessary to mitigate the robust proinflammatory response.5,19,25

The primary strengths of this case series are that it demonstrates the feasibility and efficacy of aggressive interventions for severe noninfectious ALAD and establishes a framework for standardized assessment and management of these critically ill patients.

There are several limitations to our study. First, our small sample size limits generalizability of findings. Severe noninfectious ALAD is a recently identified entity with no consensus definition. We included recipients of both unilateral and bilateral lung transplants, with the provision that only allograft injury was present, because our focus was on the pragmatic management aspects of severe ALAD. Additionally, selection bias is possible; however, during the study period, all patients meeting criteria were offered support with ECMO and immunomodulatory therapy; only 1 patient opted for a palliative approach. Furthermore, we lacked a pathologic diagnosis for the majority of our cohort. There is growing data on the impact of diffuse alveolar damage and acute fibrinous organizing pneumonia on overall prognosis,21,22,26,27 Unfortunately, the majority of our patients were too ill to obtain a tissue diagnosis. Future attempts to better phenotype patients with severe ALAD of unclear etiology with the use of cytokine profiling, peripheral blood flow cytometry, gene-expression profiling, etc, may allow for improved prognostication, diagnosis, and tailored management. Finally, it is possible that the timing
of ALAD may impact outcomes, with early-onset ALAD having a more favorable prognosis.27 Our series included patients with both early and late (>2–3 mo posttransplant) ALAD, which may in part account for our improved outcomes compared to other cohorts with severe ALAD (“lung white out”). Despite the heterogeneity in severe ALAD onset, we did not appreciate superior outcomes in those with early disease.

In conclusion, this work adds to the limited experience with the management of severe noninfectious ALAD. Based on our findings, we advocate for an aggressive management strategy (Figure 2).

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