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Research Article,

Veno-Arterial Extracorporeal Membrane Oxygenation in Adults with Septic Shock

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Abstract:

Survivors and non-survivors were compared for 20 adults supported with veno-arterial extracorporeal membrane oxygenation (VA ECMO) for refractory septic shock from 2012-2018. The primary outcome was hospital survival. Secondary outcomes were ECMO associated complications and survival to decannulation. Median age was 53.5 (IQR 42.0-61.3). At ≤ 24 hours prior to cannulation, median SOFA score was 17.5 (IQR 15 - 19) and 17 patients (85%) had new cardiac dysfunction. Median left ventricular ejection fraction (LVEF) was 20% (IQR 10-38). Thirteen patients had a mixed (cardiogenic and distributive) or cardiogenic shock profile (65%), 7 had a distributive shock profile (35%), and 17 (85%) survived to decannulation. Fourteen (70%) survived to hospital discharge and median cerebral performance category score was 1 (IQR 1-2). No differences were found in age, comorbid conditions, time from shock onset to cannulation, peak flow rate on ECMO, ECMO complications, shock profile, LVEF, or vasoactive-inotrope score (VIS). More patients in the distributive shock profile experienced limb ischemia complications (n=3, 42.9%) compared to the cardiogenic and mixed shock profiles (n=1, 7.7%). Survivors to hospital discharge had a lower SOFA score. VA ECMO support may be a beneficial therapy for refractory septic shock and could be considered in select adult patients.

Keywords: extracorporeal membrane oxygenation, organ dysfunction scores, septic shock, sepsis, survival, venoarterial extracorporeal membrane oxygenation

Introduction:

Severe sepsis and septic shock in hospitalized critically ill patients is associated with significant mortality between 10-40% and high health care costs.[1,2] Adults with fulminant infections may develop multi-organ failure despite all attempted standard treatments and often require veno-arterial extracorporeal membrane oxygenation (VA ECMO).[3] VA ECMO therapy is commonly used for temporary cardiorespiratory support until recovery from the acute incident or to allow for a transition to longer term therapies.[4] Supporting tissue and organ perfusion with veno-arterial extracorporeal membrane oxygenation (VA ECMO) has led to favorable outcomes in neonatal and pediatric patients with refractory septic shock and it is recommended for rescue therapy in these populations.[5-9]

Although published peer-reviewed literature on use of ECMO in adults with refractory septic shock is limited, several previous case reports describe successful use of VA ECMO in this population.[10-16] Several case series and one meta-analysis recently described use of ECMO in adult patients with septic shock that were associated with heterogeneous results of either favorable > 70% long-term survival or an unsatisfactory 21.9% survival to hospital discharge.[3,17-22]Mortality rates were commonly reported between 22-36%. Specific factors such as age < 60 years, infection control, the cannulation method, use of cardiopulmonary resuscitation, Simplified Acute Physiology Score II (SAPS II) and prealbumin values were all reported to significantly contribute to outcomes.

While historically controversial, international organization guidelines for the use of extracorporeal support now discuss septic shock as a possible indication for extracorporeal life support in adults (ECLS).[4] However, a gap in data remains regarding use of VA ECMO for septic shock in the adult population, particularly to guide patient selection and counsel patients or families about prognosis for this resource intensive treatment. The purpose of this study was to describe an adult population supported with VA ECMO for refractory septic shock and evaluate characteristics associated with favorable outcomes.

Materials and Methods:

A single center observational retrospective study was conducted in a single quaternary referral center in an urban setting with 686 hospital beds and 120 ECMO cases admitted per year. This study was approved by our Institutional Review Board (IRB) with a waiver of informed consent IRB# 1194725. Subsequently we completed extraction of electronic medical records data from our database system and manual review of medical records of eligible hospitalized patients admitted from January 1, 2012 to December 31, 2018. Patients aged 18 or older who were supported with VA ECMO for refractory septic shock as determined by clinician documentation were eligible for inclusion. Those with an opt-out research flag on record or pregnant were excluded.

Two researchers (KJ, RS) independently reviewed charts for inclusion and exclusion criteria and disagreements were resolved by consensus. Missing or incomplete data following database extraction were reviewed and collected manually using a data extract guide prepared by authors KJ and RS. Hemodynamic profiles were determined by clinicians with critical care expertise using chart data in the 24 hours prior to cannulation. Clinician documentation, physical exam findings and hemodynamic measurements were considered for each shock profile (Table I).[23,24]In cases where hemodynamic measurements to confirm shock type was incomplete, reported exam findings and clinician documentation were used to determine shock profile. The primary outcome was in-hospital survival. Secondary outcomes were ECMO associated complications and survival to decannulation.

Table I. Shock profile definitions used in this research study.

Shock Profile	Definition
Distributive	Hypotension, SBP < 90 for at least 30 minutes (or requiring vasopressor to maintain SBP > 90) with vasodilation and impaired organ perfusion (altered mentation, oliguria, elevated lactate). Hemodynamics with preserved CI with low SVR < 800.
Cardiogenic	Hypotension, SBP < 90 for at least 30 minutes (or requiring vasopressor or maintain SBP > 90) with vasodilation and impaired organ perfusion with pulmonary congestion and/or elevated filling pressures and impaired organ perfusion (altered mentation, oliguria, cold or clammy skin, oliguria, elevated lactate. Hemodynamics with reduced CI (< 1.8 unsupported or < 2.4 supported with high SVR > 1200, PCWP > 12).
Mixed	More than one shock type is present.
Other	Charts were reviewed for documentation or clinical evidence of hypovolemic, hemorrhagic, anaphylactic, neurogenic or obstructive shock states.

CI: Cardiac Index (L/min/m^2), PCWP: pulmonary capillary wedge pressure (mmHg), SBP: systolic blood pressure (mmHg), SVR: systemic vascular resistance (dynes*sec/cm^5).

All patients were managed using centrifugal pumps (Cardiohelp, Maquet, Rastatt, Germany; Centrimag, St Jude Medical, St. Paul, MN; Rotaflow, Maquet). VA ECMO flow was titrated to meet metabolic needs with the goal of oxygen delivery to oxygen consumption ratio greater than three or arterial oxygen saturation > 95% and mixed venous saturation > 75%. Hemoglobin levels were maintained at > 7g/dl. Anticoagulation was administered to target therapeutic levels. In cases where heparin was contraindicated, alternative continuously infused anticoagulants were used. Patients were monitored for limb oxygen saturation changes, hemolysis, secondary infection and left ventricular distention serially. Limb reperfusion catheters were placed if changes in perfusion were noted. Lung protective settings to target plateau pressure of < 25 mm Hg and a driving pressure of < 15 mm Hg were used for mechanical ventilation. Vasoactive medications were used to target mean arterial pressure > 65 mm Hg and < 90 mm Hg with additional treatments to optimize fluid balance if needed.

Statistical and Data Analysis:
Medians and interquartile ranges, proportions, and counts were calculated for patients' characteristics and outcome variables for the group of patients who survived to discharge from the hospital and the group of patients who did not survive their hospital stay. Patients with missing data were excluded from statistical analyses. Fisher's exact and Mann-Whitney tests were conducted as appropriate to compare the variables across the two survival groups. A logistic regression model was fitted using Firth's bias-Reduced penalized-likelihood method to assess the relationship between body mass index (BMI) and survival while controlling for initial SOFA score.

Results:
A search of electronic health records (EHR) was performed and we obtained 23 eligible patients. After further chart review, three patients were excluded because of not meeting the inclusion criteria (Figure 1). Baseline characteristics, hemodynamic profiles, and VA ECMO treatment variables of the 20 patients included in the study are listed in Table II. One patient transitioned from peripheral to central VA ECMO with femoral artery and vein cannulation as initial support. The remainder of patients were supported with peripheral cannulation. Of the two patients supported with veno-arterio-venous (VAV) ECMO, one had this method as the initial mode of support and another had peripheral arterial cannulation added to veno-venous (VV) ECMO support. VV ECMO was used in transition off from VA ECMO in four additional patients. All patients were supported with a single oxygenator in circuit and single pump. Determination of the shock profile in 12 patients included use of variably incomplete data on cardiac output or index, systemic vascular resistance, central venous pressure or pulmonary artery occlusion pressure in the 24 hours prior to cannulation while eight patients did not have these measurements available. A single patient had no echocardiogram data prior to VA ECMO cannulation but hadhemodynamic measurements including cardiac output, cardiac index, pulmonary artery occlusion pressure and systemic vascular resistance. Additional details of echocardiogram and hemodynamic data are shown in Table III.

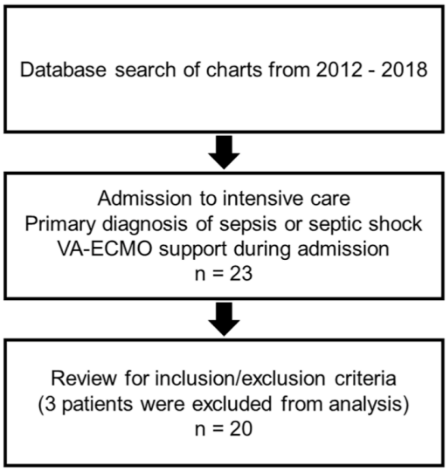

Figure1. Selection of eligible patients who were included in the study. The final number selected was 20 patients.

Table II. Clinical characteristics of hospitalized patients treated with VA-ECMO

Patient Characteristics	**Measures**
Total, n	**20**
Age in years, median (IQR)	**53.5 (42.0 - 61.3)**
Male sex, n (%)	**9 (45%)**
BMI median (IQR) kg/m^2	**27.2 (20.2 - 34.2)**
Comorbidities, n (%):	
Chronic kidney disease	**1 (5%)**
Lung disease	**4 (20%)**
Immunosuppression	**2 (10%)**
Heart failure	**1 (5%)**
Liver disease	**2 (10%)**
Echocardiogram findings in the 24 hours prior to VA cannulation:	
*LVEF prior to VA-ECMO, median% (IQR)	**20 (10 - 38)**
New cardiac dysfunction, n (%)	**17 (85%)**
LVEF ≤ 25%, n (%)	**10 (50%)**
Severe right heart failure, n (%)	**8 (40%)**
VA-ECMO characteristics:	
Time of shock onset to VA-ECMO, hours (IQR)	**13.6 (8.8 - 24.3)**
Duration of VA-ECMO, hours (IQR)	**104.9 (74.1 - 155.0)**
Peak flow in liters per minute, median (IQR)	**5.8 (5.1 - 6.6)**
VA-ECMO as initial support, n (%)	**18 (90%)**
VAV-ECMO, n (%)	**2(10%)**
VV-ECMO continued/initiated in transition off from VA-ECMO, n (%)	**6 (30%)**
Cardiac arrest prior to cannulation	**1 (5%)**
Shock profile:	
Cardiogenic, n (%)	**4 (20%)**
Distributive, n (%)	**7 (35%)**
Mixed, n (%)	**9 (45%)**
SOFA score 24 hours prior to cannulation, median (IQR)	**17.5 (15 - 19)**

BMI: body mass index, IJ: internal jugular, *LVEF: left ventricular ejection fraction, included n=19 as one patient had hemodynamic measurements but did not have recorded echocardiogram data prior to cannulation (LVEF 10% post VA ECMO cannulation), SOFA: sequential organ failure assessment, VA-ECMO: venoarterial extracorporeal membrane oxygenation, VAV-ECMO: venoarterial-venous extracorporeal membrane oxygenation, VV-EMCO: venovenous extracorporeal membrane oxygenation.

Table III. Available data for hemodynamic measurements and select echocardiogram data for patients in the 24 hours prior to cannulation, (n = 20).

Shock Profile	**Measurement Modality**	**CO**	**CI**	**SVR**	**SVRI**	**PAOP**	**LVEF**	**RVEF**
mixed	echocardiogram	6.9	3.1				25	normal
cardiogenic	echocardiogram	3.1	1.7				10	severely reduced
cardiogenic	PAC	3.46	1.9	1708	3123	28		

~distributive							45	mildly reduced
~mixed							35	severely reduced
cardiogenic	PAC	3.73	1.89	1458	2878		35	mildly reduced
~distributive	NIV	9.1	3.1				15	severely reduced
distributive	echocardiogram	5	2.9				80	normal
~distributive	NIV, echocardiogram	5.6, 4.3	3.4, 2.6	613	1023		50	normal
mixed							15	mildly reduced
distributive							80	normal
mixed	NIV, echocardiogram	8.7, 3.2	3.7, 1.4				10	severely reduced
~distributive							55	normal
mixed	PAC	2.6	1.9			32	5	severely reduced
~cardiogenic	PAC, echocardiogram	2.62, 2.2	1.39, 1.1	2286	815	26	10	severely reduced
mixed							15	moderately reduced
mixed							30	severely reduced
distributive	NIV	6.2	2.7	606	1417		30	mildly reduced
mixed							15	moderately reduced
mixed	NIV, echocardiogram	4, 3.3	2.7, 2.2	865	1289		36	moderately reduced

~VV was used at the same time, continued or started in transition from VA support. CI: cardiac index (L/min/m^2), CO: cardiac output (L/min), LVEF (%): left ventricular ejection fraction, NIV: non-invasive cardiac output monitor using Flotrac brand system, PAC: pulmonary artery catheter as Fick calculation, PAOP: pulmonary artery occlusion pressure (mmHg), RVEF: right ventricular ejection fraction. Pt. ID: each patient is labeled by an anonymous unique identification number, SVR: systemic vascular resistance (dynes*sec/cm^5), SVRI: systemic vascular resistance index (dynes*sec/cm^5/m^2). The most common shock profile was mixed. All patients in this group were considered to have a combination of cardiogenic and distributive shock. The vasoactive-inotrope score (VIS) in the 24 hours prior to cannulation was 31.6 (IQR 19.7 - 55.1).[25] The median phenylephrine dose during this time frame was 150 mcg/minute (IQR 100-200). The median lactate level was 5.2 mmol/L (IQR 3.6-8) and median troponin level was 0.21 ng/mL (0.05-0.51). Pneumonia was the most common source of infection (n = 14, 70%), bacteremia was present in 13 patients (65%). Additional infection related variables are shown in Table IV. Broad spectrum antibiotics were universally administered before or on intensive care unit (ICU) admission and during ECMO support. Additional antibiotic data is available in Supplemental Appendix I.

Table IV. Infection characteristics of patients receiving ECMO support, (n = 20).

Primary Infection	Secondary Infection(s)	Bacteremia
Pneumonia:		
MSSA	-	No
Group A streptococcus	-	Yes
Group A streptococcus - Empyema	-	Yes
Group A streptococcus	-	Yes
Unclear etiology	Clostridium difficile Candida (not speciated, bronchial fluid)	No
Legionella	-	No
Legionella	-	No
Influenza A	Lichtheimiacorybiferia (sputum) MRSA (sputum), Gram negative bacilli (not speciated, sputum)	Yes
Escherichia coli	Candida glabratafungemia	No
Streptococcus pneumoniae	MSSA (sputum) Pseudomonas aeruginosa (sputum), Clostridium difficile	Yes
Streptococcus pneumoniae Streptococcus pneumoniae	- -	Yes Yes
Pseudomonas aeruginosa	-	Yes
Urinary Tract:		
Klebsiella	-	Yes
Escherichia coli & Streptococcus	-	Yes
Escherichia coli	-	Yes
Skin or Soft Tissue:		
Parvimonasmicra - Necrotizing fasciitis	Yeast (not speciated, tissue) Coagulase negative staphylococcus (not speciated, tissue)	Yes
Unclear etiology - Lower extremity cellulitis	-	No
Intra-abdominal		
Enterocolitis - unclear etiology	-	No
Other:		
MSSA ICD infection with endocarditis, discitis, osteomyelitis	-	Yes

ICD: implantable cardioverter-defibrillator, MRSA: methicillin resistant staphylococcus aureus, MSSA: methicillin sensitive staphylococcus aureus. Pt. ID: each patient is labeled by an anonymous unique identification number

A total of 17 patients (85%) survived to decannulation from VA ECMO support. Fourteen patients (70%) survived to hospital discharge with a median cerebral performance category (CPC) score of 1 (IQR 1-2) on discharge. There was no difference in survival to hospital discharge between patients with distributive shock compared to those with mixed and cardiogenic shock (71.4% and 69.2%, $p > 0.99$) nor between those with cardiogenic shock alone compared to those with a distributive and mixed profile (68.8% and 79.2%, $p > 0.99$). There was no difference in hospital survival between those with preserved compared to decreased cardiac output in the patients with hemodynamic measurements documented in the 24 hours prior to cannulation (83.3% and 66.7%, $p > 0.99$). No patients underwent extracorporeal cardiopulmonary resuscitation. Brief pulseless electrical activity cardiac arrest occurred in one patient who had return of spontaneous circulation prior to cannulation. Fifteen non-fatal ECMO related complications were documented in 11 patients (55%) with multiple complications occurring in three patients. Hemorrhage requiring more than two units of blood product administration was most common (n = 6, 30%) followed by limb ischemia (n = 4, 20%), vascular injury (n = 2, 10%) and insertion site infection (n = 2, 10%). Ischemic or hemorrhagic stroke was uncommon (n = 1, 5.0%).

Below the knee amputation was required in one patient related to limb ischemia despite placement of a reperfusion catheter, one patient required fasciotomy, while vascular stenting or repair was required in two others. The complication rate was not statistically different between survivors and non survivors, shock profiles or those with preserved compared to decreased cardiac output. Although it did not reach statistical significance, a larger proportion of patients in the distributive shock profile experienced limb ischemia complications (n = 3, 42.9%) compared to the cardiogenic and mixed shock profiles (n = 1, 7.7%, p = 0.101).

Compared to non survivors, patients surviving to hospital discharge had a significantly lower median SOFA score in the 24 hours prior to cannulation, (Figure 2). No significant differences between these groups were seen in the following 72 hours. There were no significant differences in SOFA scores between the shock profile groups in the 24 hours prior to cannulation or in the first 72 hours of support. Similarly, no differences in SOFA scores were found between those with preserved compared to decreased cardiac output during the same time frame.

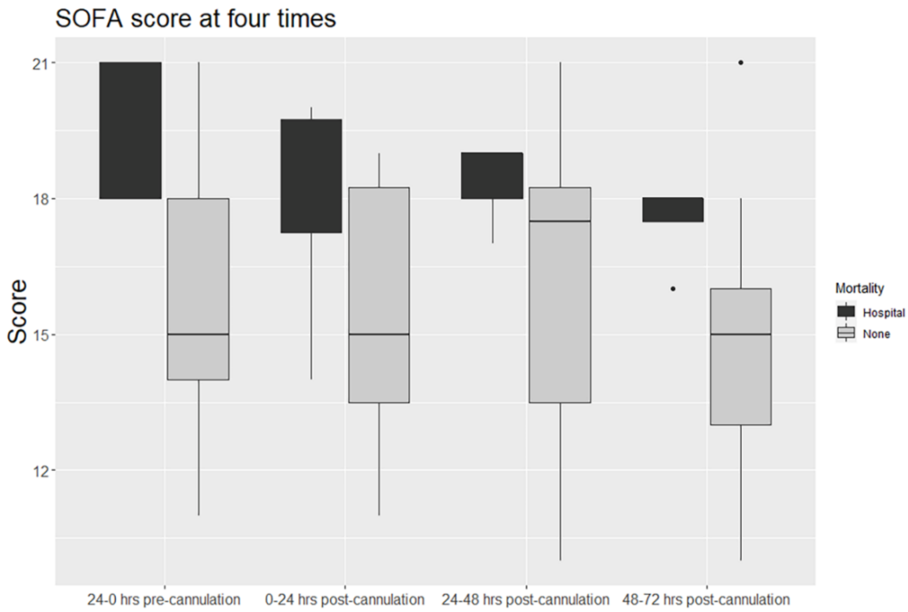

Figure 2. SOFA scores of survivors and non-survivors at four time points of pre- and post-cannulation during patients' hospitalization.

Survivors had a lower median BMI (survivor median = 22.3 kg/m^2, IQR = 19.9-28.8 and non-survivor median = 33.0 kg/m^2, IQR = 29.9-37.9; p = 0.0326). When controlling for initial SOFA score there remained a non-significant trend associating lower BMI with survival. There were no differences in age, comorbid conditions, time from shock onset to cannulation, peak flow rate on ECMO, duration of ECMO support, bacteremia, VIS, LVEF, lactate or troponin level in the 24 hours prior to cannulation between survivors and non survivors. With the exception of LVEF, there were no differences in these variables between shock profile groups (distributive profile LVEF = 42%, IQR = 25-75 compared to cardiogenic and mixed profile LVEF = 11%, IQR 10-20, p = 0.006).

While not statistically significant, a greater proportion of those with distributive shock were supported with VV ECMO in addition to or in transition from VA ECMO compared to cardiogenic and mixed groups (57.1% and 15.4%, p = 0.12). Similarly, in the 12 patients with hemodynamic data in the 24 hours prior to cannulation, there were no differences in these variables with the exception of LVEF (decreased CO/CI LVEF = 10% and preserved CO/CI LVEF = 30.5%, p = 0.022).

Discussion:

Historically sepsis has been a contraindication to ECLS support in adults due to concerns of poor prognosis as well as the uncertainty about providing adequate support for patients with distributive physiology and cellular dysfunction associated with septic shock.[26] In our study, we found an acceptable hospital mortality rate despite a severely ill population with a high predicted mortality.[27] Importantly, the majority of patients had mild disability by CPC measurements at discharge. Several factors may have contributed to the survival rate including patient and ECLS support characteristics. First, we confirmed previous findings of the prognostic value of SOFA score and organ failures prior to cannulation.[3,18,20,22] We chose to use the time frame of 24 hours prior to cannulation as a pragmatic choice, with the hope of representing patients during progression or peak severity of illness and at a point when clinicians may be contemplating ECLS support. Similar to Park et al., non-survivors trended toward higher organ failure scores at 48-72 hours after ECLS support but in our study did not reach significance. Second, only one patient in our series had cardiac arrest which has been associated with poor prognosis in two previous studies.[3,17]although there was no significant difference in age between survivors and non survivors, overall we had a young cohort. Advanced age has been found as an independent predictor of mortality in general ECMO patients and has been variably associated with mortality in patients with refractory septic shock treated with VA ECMO.[22] We confirmed previous findings of high overall survival rates for patients with left ventricular failure or cardiogenic shock profile.[18,20,21]intuitively, the reversal of low cardiac output state with initiation of ECLS restores adequate tissue oxygen delivery and may stabilize or improve organ dysfunction. Low cardiac output pathophysiology and/or low LVEF was found to be primarily or in part contributing to the shock state in the majority of our cases. In addition to patients with cardiogenic or mixed shock, patients in this series with a distributive shock profile had excellent overall hospital survival with no difference in survival compared to those with cardiogenic and mixed shock despite having a higher proportion of limb ischemia complications. Falk et al., who found a survival rate of 66.7% in patients with preserved LVEF treated with VA ECMO for septic shock, posited that patients with distributive shock may benefit from improved tissue oxygenation with support despite an inability to directly reverse vasoplegia or mitochondrial dysfunction. Interestingly, VA ECMO patients in the Falk et al. study had significantly higher flow rates than those treated with VV ECMO as initial support, the majority of which were ultimately transitioned to VA. The authors did not comment on the specific characteristics of ECLS support, such as flow rate, on survival. Characteristics of ECLS support in this case series may have been a factor. The time from shock onset to cannulation was short; a median time of 13 hours. It is possible that early support with ECLS to restore adequate tissue oxygenation may have prevented progression to irreversible organ dysfunction while source control and antimicrobial treatments had time to be effective. At least one previous study supports this, finding a delay in cannulation of more than 30.5 hours after shock onset associated with mortality.[3] Additionally, peak flow rates were comparable to flow rates reported by Falk and Brechot et al. which described excellent outcomes for patients with normal LVEF and decreased LVEF, respectively. Higher flow rates have been associated with improved survival in pediatric patients with refractory septic shock but data remains limited in adult populations.[26] Peak flow rates in the aforementioned and current studies were generally higher by up to two or more liters per minute than in Huang and Park studies who reported lower survival rates, although this may be confounded by the high proportions of cardiac arrest in the latter studies. Interestingly, after controlling for severity of illness, a trend remained associating a lower BMI with survivors while there were no significant differences in peak flow rate or time of shock onset to cannulation on ECLS support. We speculate that lower BMI patients likely had higher levels of oxygen delivery per each unit of body mass than those with higher BMI which may equate to better ECLS support in those with septic shock physiology. Due to the retrospective nature and incomplete data in medical record, further robust analysis of this finding was not able to be completed. The hypothesis merits additional study.

There are several limitations associated with our work. As in any retrospective study, there may be unmeasured or unknown variables that guided patient selection or affected survival. In addition, a clinician's ability to predict cardiac output is error prone even when using a combination of data including hemodynamic measurements, examination findings, and laboratory or imaging studies.[28] Many patients in our cohort had missing or incomplete hemodynamic assessments prior to cannulation and, despite best efforts at determining an accurate shock profile for each patient, some may have been miscategorized. A sizable number of patients were supported with VV ECMO in addition to or in transition from VA ECMO and it is possible some of this group may have done well with VV ECMO alone. The expected higher survival in VV ECMO compared to the general VA ECMO population may account in part for the overall high hospital survival rate in this cohort. Given the small sample size of our series, analysis of survival effect on characteristics was limited.

Generalizability of findings to other institutions was limited by the single center retrospective design as other centers' ECLS volume and management practices may differ.

Conclusion:

During the last decade, growing evidence has emerged for the use of VA ECMO in adults with refractory septic shock. Our study supports this practice by demonstrating acceptable mortality rates and hospital discharge level of disability. Patients with distributive shock may have higher rates of limb ischemia which should be considered when making treatment decisions. Further prospective studies investigating the relationship of patient and ECLS support characteristics on mortality in this population are needed.

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Appendix

Supplemental Appendix I. Antimicrobial data for patients receiving ECMO support, (n = 20).

Pt.	Antimicrobials/Dates of Administration	Primary Infection
1	Cephazolin 11/27-12/6, 12/15-1/17 Pipercillin-Tazobactam 11/27-11/27 Vancomycin 11/28-12/5, 1/2-1/11 Nafcillin 12/6-12/14 Gentamicin 12/5-12/13 Cephalexin 1/17-1/24	Intracardiac defibrillator infection with MSSA endocarditis, bacteremia, osteomyelitis, discitis, septic arthritis
2	Cefazolin 1/8-1/15 Cefepime 1/5-1/8 Ciprofloxacin 1/5-1/7 Vancomycin 1/5-1/7	MSSA pneumonia
3	Pipercillin-Tazobactam 2/10 Vancomycin 2/10-2/11 Imipenem-Cilastin 2/10-2/13	Klebsiella urinary tract infection, bacteremia

	Ciprofloxacin 2/10-2/13	
4	Vancomycin 12/29-12/30, 1/6-1/28 Levofloxacin 12/29-12/30 Clindamycin 12/30-1/4 Ceftriaxone 12/29-1/4 Cefepime 12/29 Pipercillin-Tazobactam 1/6-1/13	Group A streptococcal bacteremia, Pneumonia
5	Cefepime 12/16-12/17, 12/23-12/31 Clindamycin 12/18-12/26 Imipenem-Cilastin 12/18-12/23 Levofloxacin 12/16 Vancomycin 12/16-1/17 Osletamivir 12/16-12/22 Nystatin 12/31-1/6 Pipercillin-Tazobactam 1/15-1/17	Influenza A , MRSA pneumonia
6	Cefepime 12/19 Clindamycin 12/19-12/24, 1/2, 1/12 Imipenem-cilastin 12/19-1/3 Levofloxacin 12/19 Vancomycin 12/19-12/2, 1/16-2/2 Piperacillin-Tazobactam 1/17-2/4 Ampicillin-Sulbactam 1/3-1/17 Fluconazole 1/15-2/4	Necrotizing faciitis with Parvimonasmicra bacteremia
7	Azithromycin 12/9-12/9 Ceftriaxone 12/9-12/20 Clindamycin 12/11-12/31 Levofloxacin 12/9-12/12 Penicillin G 12/11-1/8 Pipercillin-Tazobactam 12/10-12/11 Vancomycin 12/10-12/11	Group A streptococcal pneumonia with empyema, bacteremia
10	Cefepime 9/22-10/5 Vancomycin IV 9/22-10/3 Levofloxacin 9/22-9/22 Doxycycline 9/23-10/2	Pneumonia, unclear etiology
11	Caspo 5/18 Imipenem 5/18-6/9 Levofloxacin 5/18 to 6/5 Vancomycin 5/18 -5/21, 6/3-6/4 Cefepime 6/10-6/26	Pseudomonas pneumonia, bacteremia
12	Ceftriaxone 4/25 -5/08 Vancomycin 4/25-4/27 Ciprofloxacin 5/09-5/23 Ertapenem 5/09-5/23 Acyclovir 5/07-5/15	Streptococcus pneumoniae bacteremia
13	Cefazolin 12/4 Cefepime12/4-12/18 Ceftriaxone 12/3 Imipenem 12/3 Vanco 12/2-12/8 Metronidazole 12/3-12/5 Ciprofloxacin 12/18-12/19	Pneumococcal pneumonia
14	Vancomycin 4/13-4/15 Levofloxacin 4/14/15 Imipenem/Cilastatin 4/13-4/14 Ceftriaxone 4/14-4/15	Pneumococcal pneumonia

15	Cefepime 9/22 Levofloxacin 9/22-10/9 Vancomycin 9/22-9/24 Azithromycin 9/22-10/04 Rifampin 9/22-9/27	Legionella pneumonia
16	Ciprofloxacin 2/20 Vancomycin 2/20-2/24 Cefazolin 2/20 Metronidazole 2/20-3/1 Caspofungin 2/20-2/22 Ceftriaxone 2/20-2/28	Enterocolitis
17	Doxycycline 8/16 Imipenem-cilastin 8/16-8/26 Levofloxacin 8/16-9/2 Pipercillin-tazobactam 8/16 Vancomycin 8/16	Legionella pneumonia
18	Ceftriaxone 11/30-12/13 Clindamycin 11/29-12/08 Imipenem-cilastin 11/29 Levaquin 11/29 Vancomycin 11/29-12/03 Cefazolin 11/29, 12/1, 12/6 Cefepime 11/29	Group A streptococcus pneumonia, bacteremia
19	Cefepime 4/12-4/14 Vancomycin 4/13, 4/21-4/23 Ceftriaxone 4/13-4/20, 4/28-4/30 Cefazolin 4/16 Pipercillian-Tazobactam 4/21-4/28	Escherichia coli urinary tract infection, bacteremia
20	Cefepime 2/13-2/26 Clindamycin 2/13-2/20 Vancomycin 2/13 -2/17, 3/1 Ciprofloxacin 3/01 Cefepime 3/1	Streptococcal cellulitis
22	Cefepime 6/30-7/2 Vancomycin 6/30-7/2 Metronidazole 6/30	Escherichia coli pneumonia
23	Ciprofloxacin 1/27 - 1/28 Meropenem 1/27-1/29 Vancomycin 1/27-1/31 Clindamycin 1/28 Ceftriaxone 1/30-2/6 Cefuroxime 2/7-2/8	Streptococcal bacteremia, Escherichia coli urinary tract infection, bacteremia