Venovenous extracorporeal membrane oxygenation for treating very severe pneumonia in Aotearoa New Zealand: a 16-year experience

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ABSTRACT

AIM: We sought to describe the aetiology, demographics and outcomes of patients with pneumonia undergoing venovenous extracorporeal membrane oxygenation (VV-ECMO) in Aotearoa New Zealand.

METHODS: Retrospective observational study.

RESULTS: Between January 2004 and August 2020, 133 patients underwent VV-ECMO for pneumonia. This VV-ECMO cohort is representative of the geographic and ethnic distribution of the population of Aotearoa New Zealand. Six-month survival was 85/133 (64%). A primary viral aetiology was identified in 63/133 cases (47%) with bacterial co-infection present in 34/63 viral pneumonias (54%). Primary bacterial pneumonia was identified in 48/133 cases (36%). Twenty-three (17%) of 133 patients developed necrotising pneumonia. The most commonly identified microorganisms were influenza A, *Staphylococcus aureus* and *Streptococcus pneumoniae*. Infection with *Staphylococcus aureus* or *Streptococcus* species was strongly associated with necrotising pneumonia (OR 10.18, 95% CI 3.52–37.13, P<0.0001). Necrotising pneumonia was more common in Māori and Pacific Peoples than in other ethnic groups (OR 3.08, 95% CI 1.16–7.96, P=0.02).

DISCUSSION: Outcomes from VV-ECMO for pneumonia in Aotearoa New Zealand are comparable to large international series. Although the use of VV-ECMO was matched to the ethnic distribution of the population of Aotearoa New Zealand, Māori may have reduced access because they have higher rates of pneumonia than non-Māori.

Pneumonia is the fourth leading cause of death worldwide.[1] In Aotearoa New Zealand, 672 deaths were attributed to pneumonia in 2018, and pneumonia was recorded as the cause of death in 0.77% of deaths in the 15–65 age group between 2015 and 2018.[2] The population of Aotearoa New Zealand is composed of multiple ethnicities, including European (62%), Māori (14%) and Pacific Peoples (7%).[3] Māori and Pacific Peoples have worse medical outcomes than Europeans, primarily due to socioeconomic disparities.[4,5] The rate of pneumonia is three times higher among Māori than non-Māori.[4]

Data on the aetiology of pneumonia in Aotearoa New Zealand are limited. A 2001 study in Christchurch and Waikato found that *Streptococcus pneumoniae* (14%), *Haemophilus influenzae* (10%), influenza A virus (7%), *Legionella* sp. (4%) and *Mycoplasma pneumoniae* (3%) were the most common causes of community-acquired pneumonia.[6] A 2008 study demonstrated viral diagnoses in 29% of patients, with rhinovirus and influenza A being the most common causative agents.[7] Sixteen percent of patients had polymicrobial infection, which was associated with worse outcomes.

Venovenous extracorporeal membrane oxygenation (VV-ECMO) is a widely accepted supportive therapy for patients with very severe pneumonia who have

a high (>50%) chance of dying despite conventional mechanical ventilation. We have previously described the physiology and cannulation options for VV-ECMO.[8,9] Briefly, blood is drained from the inferior vena cava, passed through a membrane oxygenator and returned to the right atrium. In the right atrium, oxygenated blood from the extracorporeal membrane oxygenation (ECMO) circuit mixes with the patient's systemic venous return and passes to the left heart via the pulmonary artery. Adjusting the blood flow though the ECMO circuit controls the patient's arterial oxygen tension and adjusting the sweep gas flow in the membrane oxygenator controls the patient's arterial carbon dioxide tension. Circuit blood flow and sweep gas flow of 3–8L/min can usually achieve satisfactory gas exchange, even in the absence of native pulmonary function. VV-ECMO confers two benefits in patients with acute respiratory failure. First, ECMO supports gas exchange until pulmonary function recovers. Second, ECMO allows resumption/initiation of lung protective ventilation, minimising ventilator-associated lung injury.

The Cardiothoracic and Vascular Intensive Care Unit (CVICU), Auckland City Hospital, is the national referral centre for adult ECMO in Aotearoa New Zealand. Patients referred for consideration of VV-ECMO are evaluated on a case-by-case basis according to publicly available guidelines.[10] VV-ECMO is appropriate for patients with potentially reversible lung disease who are failing mechanical ventilation. Suitable patients are assessed as likely to survive prolonged intensive care unit (ICU) stay and return to a quality of life acceptable to that patient.

ECMO is an expensive therapy and has an opportunity cost to other users of healthcare resources. There is also substantial financial and emotional cost to patients and their families inherent to the transfer to Auckland and prolonged ICU stay.

We reviewed our experience of VV-ECMO for treating patients with pneumonia to assess whether the service was effective, equitable and met the needs of the people of Aotearoa New Zealand. We wished to determine whether our pattern of ECMO use was representative of the geographic and ethnic distribution of the population of Aotearoa New Zealand. In particular, we wanted to know whether the outcome from ECMO was different for Māori and Pacific Peoples compared to other New Zealanders. Based on our clinical suspicion of poor outcome from VV-ECMO in patients with necrotising pneumonia, we assessed the outcome in this sub-group compared to other patients.

The case series largely predates the COVID-19 pandemic (and to date no patients with SARS-CoV-2 have been treated with VV-ECMO in Aotearoa New Zealand) but includes a number of patients treated during the H1N1 influenza A pandemic.

Methods

Following approval by the Auckland District Health Board Research Office, we reviewed the medical records and our in-house database of patients receiving ECMO in CVICU for suspected pneumonia between January 2004 and August 2020. Patients receiving venoarterial ECMO or VV-ECMO for reasons other than pneumonia were excluded. Data extraction was done by two authors (FM, AK).

Demographic data, along with the indications, duration and outcome from ECMO, were recorded. Microbiological and radiographic imaging results were reviewed. Necrotising pneumonia was defined by computed tomographic (CT) evidence of non-perfusion, liquefaction or cavitation of lung parenchyma.

Cause of death was defined as the primary reason for discontinuing ECMO or intensive therapies, as documented in the clinical notes or on the death certificate. Deaths occurring during or immediately following discontinuation of ECMO were recorded as a "death during ECMO." Deaths occurring after successful weaning from ECMO were recorded as a "death after ECMO."

The causative microorganism was defined as the virus or bacterial species identified prior to or within one week of hospital admission. In cases where both bacteria and viruses were identified, the virus was considered the primary infection and the bacteria considered a secondary infection. Bacterial infections were defined by a positive culture from either respi-

ratory secretions or blood. Additionally, in the case of *Streptococcus pneumoniae* (*S. pneumoniae*), a positive urinary antigen was considered diagnostic for infection. Viral infections were defined as a positive polymerase chain reaction assay from respiratory secretions.

Summary data were calculated using Excel (Microsoft Corporation, Redmond, Washington, USA). Statistical analyses were done in GraphPad Prism v 9.02 (GraphPad Software Limited, San Diego, California, USA). The relationship between infection with *Staphylococcus aureus* (*S. aureus*) or *Streptococcus* species and the development of necrotising pneumonia was investigated using logistic regression. Similarly, the relationship between Māori and Pacific Peoples ethnicity and the development of necrotising pneumonia was investigated using logistic regression. Predictors of six-month survival were evaluated using both simple (univariate) and multivariate logistic regression. Predictors were chosen based on clinical interest and previously identified risk factors for poor outcome, and comprised (1) age, (2) Māori and Pacific Peoples ethnicity, (3) infection with *S. aureus* or *Streptococcus* species and (4) the presence of necrotising pneumonia. In all cases, $P<0.05$ was considered statistically significant.

Results

Between January 2004 and August 2020, 133 patients underwent VV-ECMO for presumed pneumonia, of whom 76/133 (57%) were male and 131/133 (98%) were under 65 years old. The median age was 39 years (interquartile range [IQR] 27–52 years), with an even distribution across ages groups (Table 1).

Approximately one-third of patients were from the greater Auckland area (Auckland, Counties Manukau and Waitematā), with Canterbury, Waikato and Capital and Coast district health boards (DHBs) each contributing approximately 10% of patients (Table 2).

Median duration of ECMO support was 246 hours (IQR 150–426 hours). Six-month survival was 85/133 (64%), with 40/48 deaths (83%) occurring during ECMO (Table 3). Eighty-five (91%) of 93 patients who were successfully weaned from ECMO were alive at six months, with all survivors discharged from hospital. Death was predominantly due to non-recovery of lung function 17/48 (35%), sepsis 17/48 (35%) and neurological dysfunction 8/48 (17%). For non-survivors, the median time to death was 367 hours (IQR 139–689 hours). Survival by sub-groups is summarised in Table 3. Over half of patients had a pre-existing co-morbidity and 41/133 (31%) had a history of current

Table 1: Demographics.

	N	%
Gender		
Male	76	57
Female	57	43
Total	133	
Age		
<16	6	4.5
16–29	34	25.6
30–49	53	39.8
50–65	38	28.6
>65	2	1.5

Table 1: Demographics (continued).

	N	%
Ethnic groups		
European	78	59
Māori	24	18
Pacific Peoples	8	6
Asian	19	14
MELAA	2	1.5
Other ethnicity	2	1.5
Ethnicity		
African	1	0.8
Asian NFD	1	0.8
Chinese	6	4.5
Cook Island Māori	4	3.0
Fijian	2	1.5
Indian	9	6.8
Māori	17	12.8
Middle Eastern	1	0.8
Niuean	1	0.8
New Zealand European	74	55.6
New Zealand Māori	3	2.3
Other Asian	2	1.5
Other European	4	3.0
Samoan	3	2.3
South East Asian	1	0.8
Tongan	2	1.5
Unknown	2	1.5

MELAA: Middle Eastern/Latin American/African.

or prior smoking. Survival was similar for patients with co-morbidities (Table 3).

Viral pneumonia occurred in 63/133 patients (47%), with influenza A and B being the most common causative agents (Table 4). Pandemic H1N1 was identified in 27/47 influenza A cases (57%). Thirty-four of 63 patients (54%) with viral pneumonia had bacterial co-infection. In the majority of cases, bacterial co-infection was with *S. pneumoniae*, *S. aureus* or both. Primary bacterial pneumonia occurred in 48/133 patients (36%), with *S. aureus*, *S. pneumoniae* and *Legionella* sp. accounting for 13/48 (27%), 12/48 (25%) and 8/48 (17%), respectively (Table 4). A total of 28 patients had infection with *S. aureus*, either as a primary or secondary infection; in six of these cases (21%), the infection was due to methicillin resistant strains. In 19/133 cases (14%), no causative microorganism was identified, and the diagnosis of pneumonia was made clinically.

Seventy-eight of 133 patients (59%) underwent pulmonary CT imaging, of whom 23 (30%) had evidence of lung necrosis. Eleven of 23 patients (47.8%) with necrotising pneumonia were alive at six months. Primary or secondary bacterial infection was identified in all but two cases of lung necrosis, with the most common causative microorganisms being *S. aureus* (14/23, 61%) and *S. pneumonia* (6/23, 26%). Infection with *S. aureus*, *S. pneumoniae* or

Table 2: Referring district health board.

Region	N	%
Auckland	21	15.8
Bay of Plenty	10	7.5
Canterbury	11	8.3
Capital and Coast	12	9.0
Counties Manukau	14	10.5
Hawke's Bay	3	2.3
Hutt Valley	1	0.8
Lakes	6	4.5
MidCentral	5	3.8
Nelson Marlborough	3	2.3
Northland	5	3.8
South Canterbury	3	2.3
Southern	12	9.0
Tairāwhiti	2	1.5
Taranaki	2	1.5
Waikato	10	7.5
Wairarapa	0	0
Waitematā	13	9.8
West Coast	0	0
Whanganui	0	0

S. pyogenes was strongly associated with the development of necrotising pneumonia (OR 10.18, 95% CI 3.52–37.13, P<0.0001). Māori and Pacific Peoples accounted for 44% of patients with lung necrosis but only 24% of the entire cohort (OR 3.08, 95% CI 1.16–7.96, P=0.02).

Univariate logistic regression did not identify significant predictors of six-month survival. Multivariate logistic regression showed necrotising pneumonia was predictive of mortality at six months (Figure 5). However, the area under the receiver operating characteristic curve for the multivariate model was 0.63, indicating nearly 40% of deaths were unaccounted for by the model.

Discussion

Here we report the CVICU experience of using VV-ECMO for severe pneumonia over a 16-year period. Prior to 2004, the first year for which we have reliable data, VV-ECMO was used only sporadically in patients with pneumonia. Given CVICU serves as the national referral centre for adult ECMO, it is likely this series represents the great majority of patients treated with VV-ECMO in Aotearoa New Zealand. Our finding of 64% six-month survival is similar to that reported from large international cohorts.[11,12] Encouragingly, few patients died following successful weaning from ECMO, and patients who survived for six months were all discharged from hospital. Since ECMO is only used in patients at high risk of death with conventional treatment, it is likely our series represents a significant number of lives saved. However, it is important to acknowledge that we do not have information on quality of life or functional status—only that all survivors at six-months were out of hospital.

The cohort treated with VV-ECMO is broadly representative of the ethnic (Table 1) and geographic (Table 2) distribution of the population of Aotearoa New Zealand. One exception is the Auckland DHB, which accounted for 15.8% of cases but represents only 9.9% of the population. Māori and Pacific Peoples represent 21% of the population of Aotearoa New Zealand and accounted for 24% of people on VV-ECMO. However, Māori and Pacific Peoples are more likely to develop pneumonia and are more likely to suffer from severe disease.[4] In this context, our data suggest Māori and

Table 3: Survival and cause of death.

Survived to	**N (%)**
ECMO decannulation	93/133 (69.9)
CVICU discharge	90/133 (67.7)
Discharge from hospital	85/133 (63.9)
6-month survival	85/133 (63.9)
Aetiology of death	**N (%)**
Irreversible respiratory failure	17/48 (35.4)
Septic shock	17/48 (35.4)
Neurological injury	8/48 (16.7)
Bilateral pneumothoraces	1/48 (2.1)
Cardiac arrhythmia	1/48 (2.1)
Ischaemic bowel	1/48 (2.1)
Unknown	3/48 (6.3)

Table 3: Survival and cause of death (continued).

Ethnic group	**Survival (%)**	
European	50/78 (64)	
Māori	19/24 (79)	
Pacific Peoples	4/8 (50)	
Asian	9/19 (47)	
MELAA	2/2 (100)	
Other ethnicity	1/2 (50)	
Age	**Survival (%)**	
<16	4/6 (66.7)	
16–29	20/34 (55.8)	
30–49	36/53 (67.9)	
50–65	25/38 (65.8)	
>65	0/2 (0)	
Co-morbidities	**N**	**Survival (N)**
Respiratory*	33/133 (21.8)	19/33 (57.6)
Asthma	*18/133 (13.5)*	*9/18 (50)*
Other	*15/133 (11.3*	*10/15 (66.7)*
Diabetes	13/133 (9.7)	10/13 (76.9)
Psychiatric	18/133 (13.5)	11/18 (61.1)
Cardiovascular	24/133 (18)	16/24 (66.7)
Smoking	**N**	**Survival (N)**
	41/133 (30.8)	26/41 (63.4)
Organ failure	**N**	**Survival (N)**
Vasopressor	103/133 (77.4)	66/103 (64.1)
CRRT	58/133 (43.6)	34/58 (58.6)
Single organ Failure[+]	61/133 (45.9)	42/61 (68.8)
Multi-organ Failure	72/133 (54.1)	43/72 (59.7)
Presence of necrotic disease	23/133 (17)	11/23 (47.8)

Survival: six-month survival. *Total of asthma and non-asthma groups. +All VV-ECMO patients have respiratory failure.

Table 4: Microbiology.

Primary aetiology	N (%)	Co-infection			
		***S. aureus* N* (%)**	***S. pneumoniae* N* (%)**	***S. aureus* + *S. pneumoniae* N (%)**	**Other co-infection N (%)**
Viral	63/133 (47)	12/63 (19)	15/63 (24)	3/63 (5)	4/63 (6)
Influenza A	47/63 (75)	10/47 (21)	5/47 (11)	2/47 (4)	2/47 (4)
Influenza B	8/63 (13)	1/8 (13)	5/8 (63)		1/8 (13)
Adenovirus	3/63 (5)				
Varicella	2/63 (3)	1/2 (50)			1/2 (50)
Cytomegalovirus	1/63 (1.6)				
Human metapneumovirus	1/63 (1.6)			1	
Parvovirus	1/63 (1.6)				
Bacterial	48/133 (36)	1/48 (2)	1/48 (2)		
Staphylococcus aureus	13/48 (27)				
Streptococcus pneumoniae	12/48 (25)				
Legionella longbeachiae	4/48 (8)	1/4 (25)			
Legionella pneumophila	4/48 (8)				
Streptococcus pyogenes	3/48 (6)				
Klebsiella pneumoniae	2/48 (4)				
Mycoplasma pneumoniae	2/48 (4)				
Pseudomonas aeruginosa	2/48 (4)				
Escherichia coli	1/48 (2)				
Haemophilus influenzae	1/48 (2)		1/1 (100)		
Haemophilus parainfluenzae	1/48 (2)				
Tuberculosis	1/48 (2)				
Fungal					
Aspergillus sp.	3 (100)				
Unknown[-]	19/133 (14)				

*Not including cases where both *S. aureus* and *S. pneumoniae* were isolated—these are counted in the subsequent column. [-]Clinical diagnosis of pneumonia without positive microbiology in written notes, or in local online reporting system.

Pacific Peoples may be underrepresented in terms of VV-ECMO use.

Overall, the VV-ECMO cohort represents a young group of patients with relatively few co-morbidities (Tables 1 and 3), which probably reflects (an appropriate) selection bias against using VV-ECMO in co-morbid patients who have worse outcomes.[12]

The aetiology of pneumonia in our cohort is similar to that reported for community-acquired pneumonia in New Zealand, with a predominance of influenza A and *S. pneumoniae*.[6,7] The high rate of influenza A is in part due to 27 cases of pandemic H1N1 who required VV-ECMO. One exception to previous New Zealand cohorts and to community-acquired pneumonia in general[13] is the high incidence of *S. aureus*, which was identified in 21% of patients, either as a primary or secondary infection. This finding is unsurprising because *S. aureus* pneumonia is associated with more severe disease and worse outcomes than pneumonia due to other microorganisms.[13] At least in children, *S. aureus* sepsis is more common in Māori and Pacific Peoples than in Europeans.[14] The microbiology of *S. aureus* in Aotearoa New Zealand is notable for increased prevalence of Panton-Valentine leukocidin producing genes,[15] a cytotoxin that causes necrotising pneumonia.[16]

Necrotising pneumonia was strongly associated with infections due to *S. aureus* and streptococcal species and was more common in Māori and Pacific Peoples. The association between necrotising pneumonia and *S. aureus* and *S. pneumoniae* has long been recognised.[17,18] Although necrotising pneumonia is known to be associated a high mortality,[17,19] it was only weakly predictive of non-survival in our cohort (Table 5), which probably reflects the relatively small number of patients with this condition and selection bias against offering VV-ECMO to patients with very severe lung necrosis. However, given our clinical concern regarding futility for VV-ECMO in patients with lung necrosis, the fact that nearly half of patients with necrotising pneumonia survived for six months is reassuring.

There are several limitations to this case series. First, and most importantly, the patients included in the series represent a highly selected group. The available CVICU intensivists discuss all patients referred for ECMO and only accept the referral if there is a consensus that ECMO is likely to be beneficial. Older (>65 years) and highly co-morbid patients are typically declined. Second, the decision to discontinue VV-ECMO for futility is complex and includes factors such as the patient's disease trajectory, their likely post-ECMO functional status and organ function, the wishes of the family, the expressed views of the patient and the opinions of the treating physicians.

Table 5: Predictors of six-month survival from logistic regression.

	Univariate		**Multivariate**	
	Odds ratio (95% CI)	**P value**	**Odds ratio (95% CI)**	**P value**
Age	0.993 (0.970– 1.018)	0.610	0.987 (0.961–1.013)	0.318
Ethnicity (Māori or Pacific Peoples)	1.608 (0.692– 3.995)	0.284	1.980 (0.805–5.311)	0.152
Infection with *S. aureus* or streptococcal species	0.8159 (0.398– 1.680)	0.579	0.948 (0.422–2.177)	0.898
Necrotising pneumonia	0.4459 (0.177– 1.111)	0.082	0.330 (0.110–0.946)	0.042

CI: confidence interval.

Such factors impact upon both the duration of VV-ECMO support and overall survival. Finally, over the 16-year period of the study, the data collected, the management of VV-ECMO and the treatment of patients with very severe pneumonia have changed.

Notwithstanding these limitations, we can draw the following conclusions. First, our pattern of VV-ECMO use for severe pneumonia is representative of the ethnic and geographic distribution of the population of Aotearoa New Zealand. Second, our outcomes, which are highly dependent on patient selection, are comparable to that reported in larger, international series. Third, despite our clinical concern, VV-ECMO is an appropriate intervention for selected patients with necrotising pneumonia. Fourth, the use of and the outcome from VV-ECMO for Māori and Pacific Peoples is comparable to that of other New Zealanders. However, given their higher rates of pneumonia and, particularly, their higher rates of staphylococcal pneumonia, it is highly likely that Māori and Pacific Peoples are underrepresented in terms access to VV-ECMO.

Competing interests:
Nil.
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