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Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome

The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators*

Context The novel influenza A(H1N1) pandemic affected Australia and New Zealand during the 2009 southern hemisphere winter. It caused an epidemic of critical illness and some patients developed severe acute respiratory distress syndrome (ARDS) and were treated with extracorporeal membrane oxygenation (ECMO).

Objectives To describe the characteristics of all patients with 2009 influenza A(H1N1)–associated ARDS treated with ECMO and to report incidence, resource utilization, and patient outcomes.

Design, Setting, and Patients An observational study of all patients (n=68) with 2009 influenza A(H1N1)–associated ARDS treated with ECMO in 15 intensive care units (ICUs) in Australia and New Zealand between June 1 and August 31, 2009.

Main Outcome Measures Incidence, clinical features, degree of pulmonary dysfunction, technical characteristics, duration of ECMO, complications, and survival.

Results Sixty-eight patients with severe influenza-associated ARDS were treated with ECMO, of whom 61 had either confirmed 2009 influenza A(H1N1) (n=53) or influenza A not subtyped (n=8), representing an incidence rate of 2.6 ECMO cases per million population. An additional 133 patients with influenza A received mechanical ventilation but no ECMO in the same ICUs. The 68 patients who received ECMO had a median (interquartile range [IQR]) age of 34.4 (26.6-43.1) years and 34 patients (50%) were men. Before ECMO, patients had severe respiratory failure despite advanced mechanical ventilatory support with a median (IQR) PaO_2/fraction of inspired oxygen (FIO_2) ratio of 56 (48-63), positive end-expiratory pressure of 18 (15-20) cm H_2O, and an acute lung injury score of 3.8 (3.5-4.0). The median (IQR) duration of ECMO support was 10 (7-15) days. At the time of reporting, 48 of the 68 patients (71%; 95% confidence interval [CI], 60%-82%) had survived to ICU discharge, of whom 32 had survived to hospital discharge and 16 remained as hospital inpatients. Fourteen patients (21%; 95% CI, 11%-30%) had died and 6 remained in the ICU, 2 of whom were still receiving ECMO.

Conclusions During June to August 2009 in Australia and New Zealand, the ICUs at regional referral centers provided mechanical ventilation for many patients with 2009 influenza A(H1N1)–associated respiratory failure, one-third of whom received ECMO. These ECMO-treated patients were often young adults with severe hypoxemia and had a 21% mortality rate at the end of the study period.

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In April 2009, the Mexican Ministry of Health reported an increase in severe pneumonia cases in young adults.[1] The 2009 novel swine-origin influenza A(H1N1) virus was identified as its cause and rapidly led to a worldwide pandemic.[2] This pandemic began in the northern hemisphere during late spring and early summer and appeared to decrease in intensity within a few weeks.[3] Shortly after, at the start of the southern hemisphere winter, it spread to Australia and New Zealand causing an approximately 8-fold greater number of confirmed cases per head of population than in the United States.[4,5]

The spread of the virus to Australia and New Zealand was also associated with a large number of patients admitted to intensive care units (ICUs) across both countries.[6] A proportion of these patients presented with, or developed, severe acute respiratory distress syndrome (ARDS). In some severe cases, extracorporeal membrane oxygenation (ECMO) was commenced for the treatment of refractory hypoxemia, hypercapnia, or both, which occurred despite mechanical ventilation and rescue ARDS therapies.

We report herein on the incidence, clinical features, severity of respiratory failure, technical characteristics, duration of extracorporeal support, complications, and survival in patients with severe influenza-related ARDS who were treated with ECMO. In addition, we discuss the relevance of our findings to the potential ECMO case

For editorial comment see p 1905.

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load in northern hemisphere countries during their 2009-2010 winter.

METHODS

Study Design and Patient Eligibility

We studied adult and pediatric patients who were treated with ECMO between June 1 and August 31, 2009. We contacted all 187 ICUs in Australia and New Zealand and identified the 15 ICUs that provided ECMO support during this period. We excluded neonates or patients treated with ECMO for primary cardiac failure, following heart and/or lung transplantation or cardiac surgery. We applied these eligibility criteria to capture all confirmed or strongly suspected cases of 2009 influenza A(H1N1)–related respiratory disease. We also identified and excluded patients with an alternative diagnosis and who had no virus isolated.

All members of the binational management committee approved the study protocol. Trained research coordinators or treating clinicians used a case report form to obtain relevant data. Approval was obtained from the hospital research ethics committees at all participating centers. All committees waived the need for informed consent.

Data Collection

We collected data retrospectively on patient demographics including age, sex, height, weight, and ethnicity, as well as the presence of a number of predefined comorbidities. We assessed whether patients fulfilled criteria during the period before or at the time of presentation to hospital for an influenza-like illness based on typical symptoms[7] (defined as ≥3 symptoms of sore throat, cough, myalgia or arthralgia, respiratory distress, vomiting or diarrhea, and core temperature >38°C). We also assessed whether they fulfilled criteria for community-acquired pneumonia[8] (defined as presence of a new or progressive infiltrate on chest radiograph plus ≥2 symptoms of cough, sputum production, core temperature >38°C, auscultatory findings consistent with pneumonia, leukocytosis [>10 000/μL or >15% bands], C-reactive protein >3-fold the normal upper limit, and a positive culture from blood or pleural fluid). We identified the presumed infectious organism from upper and lower respiratory tract specimens (polymerase chain reaction, viral culture, or both), blood cultures, or urinary antigens obtained within the first 72 hours of admission, or from convalescent or paired serology testing.

We obtained information on the timing of endotracheal intubation in relation to presumed onset of symptoms and hospital admission, the total duration of mechanical ventilation, and administration of antiviral and antibiotic medications. We documented whether the ECMO treatment was commenced in the participating hospital or whether the patient was retrieved and transferred while receiving ECMO from a referral center.

We assessed severity of illness before endotracheal intubation by documenting respiratory rate and measures of oxygenation. We assessed severity of illness before commencement of ECMO by documenting nonpulmonary vital organ support, severity of hypoxemia, hypercapnia, ventilator settings, and use of rescue ARDS therapies in the 6 hours before ECMO commencement. We also obtained data to calculate a modified acute lung injury score (range, 0-4) during this period.[9]

We recorded duration of mechanical ventilation, ECMO, ICU and hospital stay, mortality, and destination at hospital discharge. Information on functional status at hospital discharge in survivors included whether the patient was ambulant and the pulse oximetry reading on room air. In patients who died during hospital admission, we characterized the mode of death from a list of predefined options.

Data on demographics, comorbidities, treatment, and outcome were collected on patients with confirmed influenza A who were not treated with ECMO in the same ICUs. The use of ECMO for ARDS in the ECMO centers during the winter of 2008 was obtained from each ICU's registry of cases.

Statistical Analysis

Data analysis was descriptive using median and interquartile range (IQR). We made no assumptions about missing data and adjusted proportions to the number of patients with available data. When acute lung injury score variables were missing, the modified score was calculated (dividing the sum of subscores by the number of known variables). To report our findings rapidly, we censored all outcomes at midnight on September 7, 2009. Using current Australia and New Zealand population data,[10,11] we calculated the incidence of ECMO use per million people for Australia and New Zealand in total, and for each jurisdiction (Australian states and New Zealand) that provided ECMO support. We also calculated the incidence of ECMO use for confirmed as well as the combination of confirmed and suspected 2009 influenza A(H1N1). We also estimated the ECMO burden by calculating the total number of days on which ECMO was provided to all patients and by calculating the total number of patients treated concurrently in all hospitals in Australia and New Zealand for each day of the winter period.

Comparisons of proportions were made using χ^2 tests for equal proportion or Fisher exact tests when numbers were small. Continuous variables were compared using Wilcoxon rank sum tests. All reported P values are 2-sided and were not adjusted for multiple comparisons. $P<.05$ was considered statistically significant. Analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient Characteristics and Use of ECMO

Between June 1 and August 31, 2009, 72 patients were treated with ECMO and fulfilled eligibility criteria for the study in the 15 participating ICUs. Four

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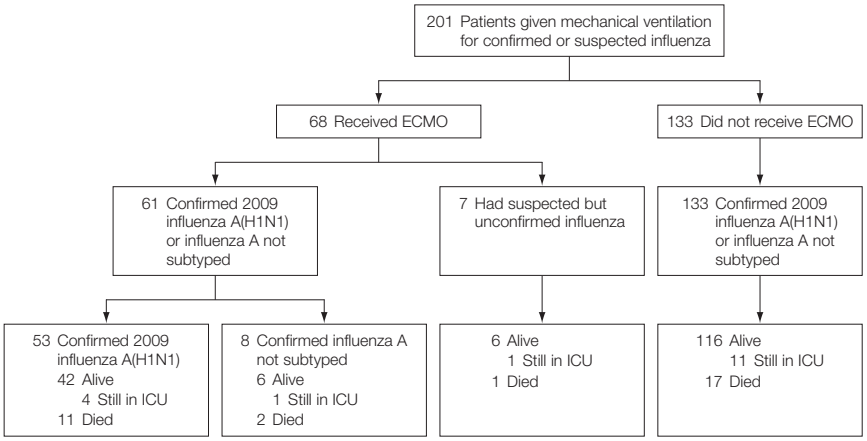
patients were excluded from analysis because 3 patients had alternative diagnoses (Wegener granulomatosis, connective tissue disease, and cystic fibrosis) and 1 patient had 2009 influenza A(H1N1)–associated fulminant myocarditis without ARDS.

For the remaining 68 patients who received ECMO, the median (IQR) age was 34.4 (26.6-43.1) years and 34 patients (50%) were men. The most common associated comorbidities were obesity (body mass index >30, calculated as weight in kilograms divided by height in meters squared), asthma, and diabetes mellitus in 34 patients (50%), 19 patients (28%), and 10 patients (15%), respectively. Six patients (9%) were pregnant and 4 patients (6%) were postpartum (<28 days of delivery). Three children (aged <15 years) and no elderly patients (aged >65 years) received ECMO.

Figure 1. Flow Diagram of Patients Receiving Mechanical Ventilation for Suspected 2009 Influenza A(H1N1) Infection at ECMO Centers



ECMO indicates extracorporeal membrane oxygenation; ICU, intensive care unit.

Table 1. Comparison of Patients With Influenza A Who Received ECMO and Those Who Received Mechanical Ventilation But Without ECMO at ECMO Centers[a]

Parameter	ECMO (n = 61)	Mechanical Ventilation But Without ECMO (n = 133)	*P* Value
Age, median (IQR), y	36 (27-45)	44 (31-54)	.02
Male sex	29 (48)	63 (47)	.54
BMI, median (IQR)	29 (23-36)	29 (24-37)	.92
Chronic lung disease	18 (30)	35 (26)	.64
APACHE III comorbidity[b]	5 (8)	30 (23)	.02
Pregnancy or postpartum	10 (16)	12 (9)	.21
Diabetes mellitus	9 (15)	23 (17)	.64
H1N1 positive	56 (92)	107 (80)	.05
At ICU admission			
Mechanical ventilation	53 (87)	117 (88)	.80
Vasopressor	35 (57)	46 (34)	.02
Renal replacement therapy	5 (8)	9 (7)	.95
Duration or length of stay, median (IQR), d			
Mechanical ventilation	18 (9-27)	8 (4-14)	.001
ICU	22 (13-32)	12 (7-18)	.001
Hospital	28 (15-43)	20 (13-31)	.07
Mortality			
in ICU	14 (23)	12 (9)	.01
in hospital	14 (23)	17 (13)	.06

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range.
[a]Data are presented as No. (%) unless otherwise specified.
[b]The presence or not of at least 1 comorbidity.

Of the 68 patients who received ECMO for influenza-associated ARDS, 66 (97%) fulfilled criteria for pneumonia and 64 (94%) fulfilled criteria for a preceding influenzalike illness. Fifty-three patients (78%) had 2009 influenza A(H1N1) detected by polymerase chain reaction or viral culture and 8 patients (12%) had serological evidence of recent influenza A that was not subtyped and was regarded as suspected to be 2009 influenza A(H1N1) (FIGURE 1). The remaining 7 patients (10%) had preceding symptoms of influenzalike illness and were also regarded as having suspected 2009 influenza A(H1N1). Seasonal subtypes of influenza A were not detected in any patient. Nineteen (28%) patients also had a secondary organism isolated from a respiratory tract specimen or blood sample at the time of hospital presentation, the most common being *Streptococcus pneumoniae* (n=10) and *Staphylococcus aureus* (n=4).

During the study period, 252 patients were admitted to the 15 participating ICUs with influenza. Of these patients, 201 received mechanical ventilation. Of the 194 patients with either confirmed 2009 influenza A(H1N1) or influenza A not subtyped, 61 treated with ECMO were compared with the 133 treated with mechanical ventilation but without ECMO in TABLE 1.

The estimated incidence of ECMO use for the combination of confirmed and suspected 2009 influenza A(H1N1) during the winter influenza season was 2.6 (95% confidence interval [CI], 2.0-3.2) cases per million people. When only confirmed cases were considered, the estimated incidence was 2.0 (95% CI, 1.4-2.6) cases per million. In the jurisdictions where patients were

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treated, the estimated incidence of ECMO use varied from 1.6 (95% CI, 1.1-2.1) to 5.3 (95% CI, 4.3-6.3) cases per million for confirmed and suspected 2009 influenza A(H1N1). The total ECMO burden for the cohort was 828 days of ECMO (32; 95% CI, 30-34 ECMO days per million). The number of patients treated concurrently with ECMO in Australia and New Zealand peaked 8 weeks after the first patient was treated and then decreased during the next 4 weeks, with the maximum number of 23 patients (34%) on 3 consecutive days in early August (FIGURE 2). In the previous winter (June 1-August 31, 2008), only 4 patients (estimated incidence of 0.15 cases per million people) received ECMO for ARDS in participating sites.

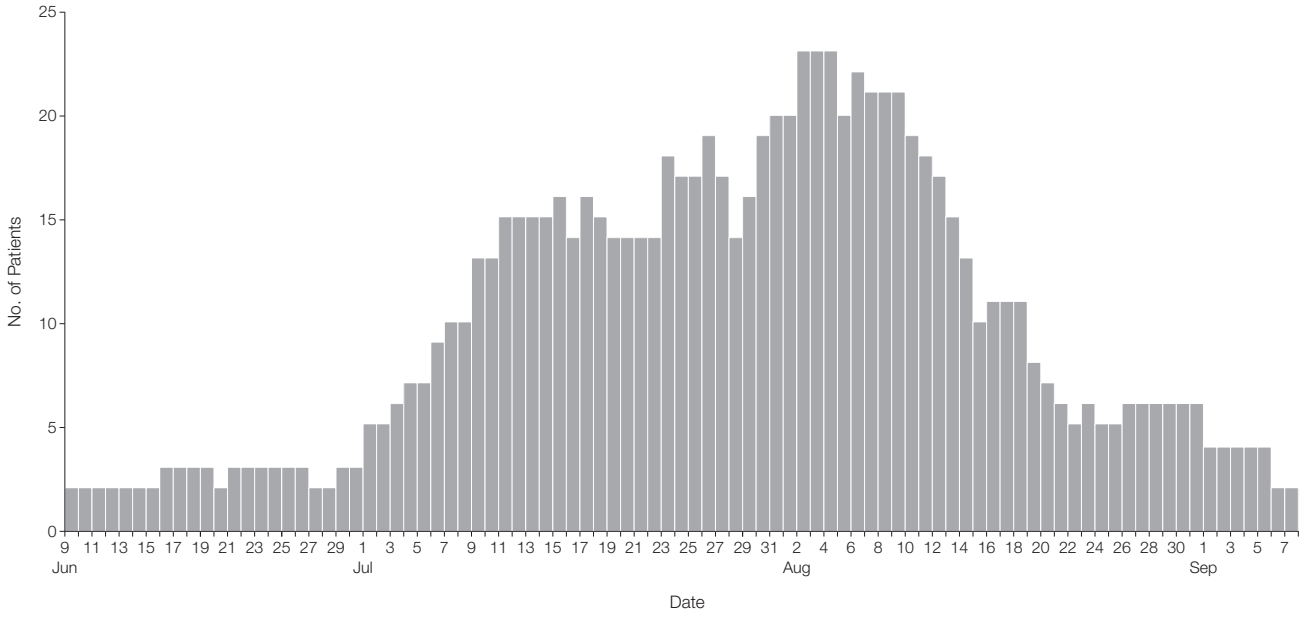
The median (IQR) interval between the onset of influenzalike symptoms and hospital admission, ICU admission, and ECMO was 5 (3-6) days, 5 (3-7) days, and 9 (5-13) days, respectively. Oseltamivir (administered enterally) was used as initial antiviral treatment in 64 patients (94%) for a median (IQR) duration of 8 (7-11) days. Forty-nine of 68 patients (72%) who received ECMO required retrieval and inter-hospital transfer to the ECMO-providing site; of these, 38 (78%) were started on ECMO at the referring site and successfully transferred while receiving ECMO.

Severity of Illness and Treatment Before Commencement of Mechanical Ventilation and ECMO

Median (IQR) duration of mechanical ventilation before commencement of ECMO was 2 (1-5) days. Before mechanical ventilation, the median (IQR) respiratory rate, arterial oxygen saturation (SaO_2), and PaO_2 were 44 (31-48)/min, 83% (77%-88%), and 53 (47-60) mm Hg, respectively. Details of severity of illness in the 6 hours before ECMO commencement are shown in TABLE 2. Overall, patients had a median (IQR) lowest PaO_2/fraction of inspired oxygen (FIO_2) ratio of 56 (48-63), a lowest pH of 7.2 (7.1-7.3), a highest $PaCO_2$ of 69 (54-83) mm Hg, and a modified acute lung injury score of 3.8 (3.5-4.0). The median (IQR) highest recorded FIO_2, positive end-expiratory pressure, tidal volume (per kg body weight), and peak airway pressure before ECMO commencement were 1.0 (1.0-1.0), 18 (15-20) cm H_2O, 5.6 (4.6-6.7) mL/kg, and 36 (33-38) cm H_2O, respectively. All but 2 patients had a PaO_2/FIO_2 ratio of 83 or less, and both of these had a $PaCO_2$ of 98 or more and a pH of 7.07 or less. All patients had either a modified acute lung injury score of 3.0 or more, or the combination of hypercapnia and a pH of less than 7.2. Representative images of a chest radiograph and a computed tomogram for these patients are shown in FIGURE 3.

In cases with available data before commencement of ECMO, clinicians used rescue ARDS therapies such as recruitment maneuvers in 38 patients (67%), prone positioning in 12 patients (20%), high-frequency oscillatory ventilation in 3 patients (5%), inhaled nitric oxide in 20 patients (32%), or prostacyclin in 14 patients (22%). Overall, 55 patients (81%) received at least 1 of these therapies. Furthermore, 46 patients (68%) received vasoactive drugs and 16 patients (24%) received renal replacement therapy before commencement of ECMO. Patients with secondary bacterial infection at the time of hospital presentation

Figure 2. Histogram of Number of Concurrent Patients Receiving ECMO Across Australia and New Zealand in 2009



ECMO indicates extracorporeal membrane oxygenation.

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(n=19) were more likely to receive vasoactive drugs (90% vs 59%, respectively; $P=.01$).

Technical Details of ECMO Support

All centers provided ECMO with centrifugal blood pump driven circuit flow and polymethylpentene low-resistance oxygenators. The initial mode of ECMO was veno-venous in 63 patients (93%) and veno-arterial in 5 patients (7%). No arteriovenous (pumpless) support was used. The median (IQR) duration of ECMO support was 10 (7-15) days. Median (IQR) circuit blood flow at 4 and 24 hours was 4.9 (4.0-5.9) and 4.9 (3.9-6.0) L/min, respectively.

All adult patients had vascular cannulae inserted through a peripheral approach into the femoral, jugular, or both vessels, and 1 child had central cannulae. In 33 patients (49%), a second access cannula was needed to augment ECMO support. Hemorrhagic complications occurred in 37 patients (54%) during ECMO therapy, with the most common sources being ECMO cannulation sites in 15 patients (22%), gastrointestinal tract in 7 patients (10%), respiratory tract in 7 patients (10%), vaginal bleeding in 6 patients (9%), and intracranial hemorrhage in 6 patients (9%).

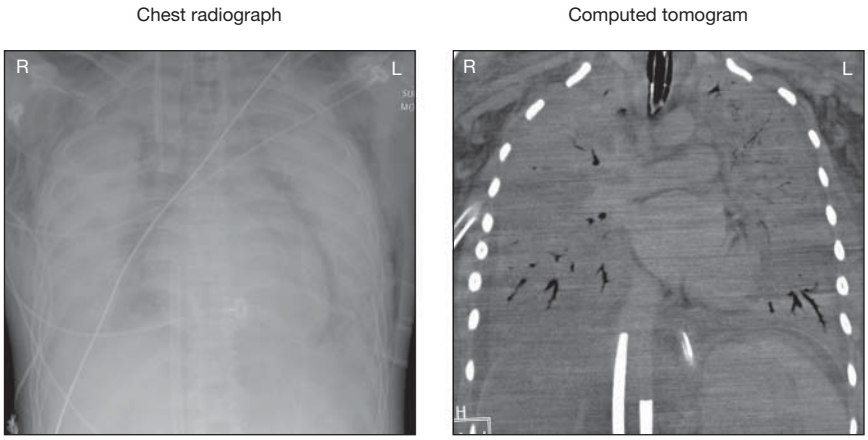
The median (IQR) amount of blood administered per patient was 1880 (904-3750) mL. Infective complications occurred in 42 patients (62%) during ECMO therapy, with the most common sites being respiratory tract in 30 patients (44%), bloodstream in 14 patients (21%), non-ECMO catheter-related in 13 patients (19%), and ECMO cannulae-related in 7 patients (10%).

Table 2. Severity of ARDS Before Commencement of ECMO

Characteristics	2009 Influenza A(H1N1) Confirmed Infection (n = 53)	2009 Influenza A(H1N1) Suspected Infection (n = 15)	All Infections (N = 68)
Ventilation parameters, median (IQR)			
Lowest Pao_2/Fio_2 ratio	55 (48-65)	57 (45-62)	56 (48-63)
Highest Fio_2	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Highest PEEP, cm H_2O	18 (15-20)	15 (14-18)	18 (15-20)
Highest peak airway pressure, cm H_2O	36 (34-40)	34 (29-36)	36 (33-38)
Lowest pH	7.2 (7.1-7.3)	7.2 (7.1-7.3)	7.2 (7.1-7.3)
Highest $Paco_2$, mm Hg	69 (54-86)	67 (61-73)	69 (54-83)
Highest tidal volume, mL/kg	5.6 (4.8-6.6)	5.7 (4.4-6.7)	5.6 (4.6-6.7)
Quadrants of radiograph infiltrate, No.	4 (4-4)	4 (4-4)	4 (4-4)
Acute lung injury score[a]	3.8 (3.3-4.0)	3.5 (3.3-3.8)	3.8 (3.5-4.0)
Pneumothorax pre-ECMO, No. (%)	9 (17)	1 (7)	10 (15)
Rescue ARDS therapies used, No. (%)			
Recruitment maneuver	30 (66)	8 (66)	38 (67)
Prone positioning	11 (22)	1 (8)	12 (20)
High-frequency oscillation	3 (6)	0	3 (5)
Nitric oxide	19 (38)	1 (8)	20 (32)
Prostacyclin	12 (23)	2 (15)	14 (22)

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; Fio_2, fraction of inspired oxygen; IQR, interquartile range; PEEP, positive end-expiratory pressure.
[a] Data were missing in 4 cases for Pao_2/Fio_2 ratio, in 4 cases for PEEP, in 17 cases for lung compliance, and in 5 cases for quadrants of radiograph infiltrate.

Figure 3. Chest Radiograph and Computed Tomogram of 2 Patients Successfully Treated With ECMO for Confirmed 2009 Influenza A(H1N1)



ECMO indicates extracorporeal membrane oxygenation. The images demonstrate severe bilateral airspace disease with massive loss of normal aerated lung tissue.

Details of ICU Support and Outcomes for Patients Requiring ECMO

The median (IQR) duration of mechanical ventilation was 25 (13-34) days (26 [14-34] and 14 [7-29] days for survivors and nonsurvivors, respectively) (TABLE 3). Tracheostomy was performed to assist weaning from mechanical ventilation in 39 patients (57%). The median (IQR) durations of ICU admission and hospitalization were 27 (16-37) and 39 (23-47) days, respectively.

Of the 68 patients, 53 (78%; 95% CI, 68%-88%) had been weaned from ECMO, 13 had died while receiving ECMO, and the other 2 were still receiving ECMO as of September 7, 2009. Of the 53 patients weaned from ECMO, 1 had died and 52 (76%) were still alive. Of the 52 patients still alive and weaned from ECMO, 4 were still in the ICU and 48 (71%; 95% CI, 60%-82%) had survived to ICU discharge. Of the 48 ICU survivors, 16 patients (24%; 95% CI, 13%-34%)

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were still in the hospital and 32 patients (47%; 95% CI, 35%-59%) had survived to hospital discharge.

Of the 32 hospital survivors, 31 patients (97%) were ambulant. In 20 of 32 hospital survivors, pulse oximetry data on room air were available and all patients had recordings of 92% or more (median [IQR], 97% [95%-98%]). In the 14 patients who died (21%; 95% CI, 11%-30%), intracranial hemorrhage (n=6), other hemorrhage (n=4), and intractable respiratory failure (n=4) were the most common conditions contributing to death. Of the 10 pregnant or postpartum patients, 7 (70%) were alive. Of the 3 children treated with ECMO, all 3 were alive; however, 1 child remained in the ICU.

Details of Outcomes for Patients With and Without ECMO

From the group of 194 mechanically ventilated patients with confirmed 2009 influenza A(H1N1) or influenza A not subtyped (not all of whom had ARDS), patients treated with ECMO (n=61) were compared with those without (n=133). The patients who were treated with ECMO had longer duration of mechanical ventilation (median [IQR], 18 [9-27] vs 8 [4-14] days; $P=.001$), ICU stay (median [IQR], 22 [13-32] vs 12 [7-18] days; $P=.001$), and greater ICU mortality (14 [23%] vs 12 [9%]; $P=.01$).

COMMENT

Summary of Study Findings

We identified all patients who received ECMO for severe ARDS during the 2009 influenza A(H1N1) winter pandemic in Australia and New Zealand. Although there are almost 200 ICUs across these 2 countries, all ECMO was provided at just 15 specialist centers. Within these centers, the burden was substantial, as highlighted by the provision of a large number of total days of ECMO support and the use of ECMO support in approximately one-third of all cases requiring mechanical ventilation at these centers. Affected patients were often young adults, pregnant or postpartum, obese, had severe respiratory failure before ECMO, and received prolonged mechanical ventilation and ECMO support. Children and elderly persons were infrequently treated with ECMO. The majority of patients underwent retrieval to a specialist center for ECMO. Despite the disease severity and the intensity of treatment, the mortality rate was low.

Comparison With Previous Studies

To our knowledge, this is the first multicenter study on the use of ECMO for 2009 influenza A(H1N1)–associated ARDS. Publications from an international ECMO registry[12] and from centers experienced in the use of ECMO for ARDS of heterogeneous etiology have reported mortality rates between 30% and 48%.[13-15] Although our patients had a mortality rate of 21% (95% CI, 11%-30%), several patients remained in the ICU at the time of reporting.

Several factors may have contributed to the observed mortality rate. First, our patients were young and had ARDS secondary to viral pneumonia, which when managed with ECMO has been associated with higher survival rates than other causes of ARDS.[12-14] Second, improvements in ECMO technology (eg, heparin-bonded cannulae, rotary pumps, and small efficient long-lasting oxygenators) and staff training have occurred since previous publications, leading to safer and more effective ECMO application. All of the patients fulfilled the ARDS severity criteria for enrollment in a recently reported randomized controlled trial (the CESAR study[16]) of ECMO treatment.

Implications for Policy Makers and Clinicians

Our findings have implications for health care planning and the clinical

Table 3. Patient Outcomes[a]

Outcome Measure	2009 Influenza A(H1N1) Confirmed Infection (n = 53)	2009 Influenza A(H1N1) Suspected Infection (n = 15)	All Infections (N = 68)
Length of stay, median (IQR), d			
ICU	26 (16-35)	31 (15-38)	27 (16-37)
Hospital	35 (24-45)	40 (27-54)	39 (23-47)
Duration, median (IQR), d			
Mechanical ventilation	24 (13-31)	28 (13-34)	25 (13-34)
ECMO support	10 (7-14)	11 (10-16)	10 (7-15)
Survival at ICU discharge	38 (72)	10 (67)	48 (71)
Still in ICU	4 (8)	2 (13)	6 (9)
Survival at hospital discharge	22 (42)	10 (67)	32 (47)
Still in hospital[b]	14 (26)	2 (13)	16 (24)
Ambulant at hospital discharge[c]	21 (95)	10 (100)	31 (97)
Sa_{O_2} on room air at hospital discharge, median (IQR), %[c]	97 (95-98)	97 (95-98)	97 (95-98)
Discharge destination			
Died	11 (21)	3 (20)	14 (21)
Home	18 (34)	4 (27)	22 (32)
Other hospital	0	1 (7)	1 (1)
Rehabilitation facility	4 (8)	5 (33)	9 (13)
Cause of death[d]			
Hemorrhage	3 (27)	1 (33)	4 (29)
Intracranial hemorrhage	4 (36)	2 (66)	6 (43)
Infection	1 (9)	0	1 (7)
Intractable respiratory failure	3 (27)	1 (33)	4 (29)

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; Sa_{O_2}, arterial oxygen saturation.
[a] Data are presented as No. (%) unless otherwise specified.
[b] Not including patients still in the ICU.
[c] For survivors only.
[d] Data are shown as No. (% of deaths) and patients could have more than 1 cause contributing to death.

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management of patients with 2009 influenza A(H1N1) during the 2009-2010 northern hemisphere winter. Our results indicate that the incidence of ARDS sufficient to warrant consideration of ECMO, based on the criteria used for the CESAR study,[16] exceeds 2.6 per million inhabitants. Given the outcomes reported in the CESAR study and in our study, other clinicians may also choose to treat these patients with ECMO. Approximately 15% of our patients were pregnant or postpartum, the largest case series of such patients in the literature.[17,18] Most of these patients survived.

Despite the additional disease burden, ECMO capacity was never exceeded; however, information on the resource utilization should facilitate planning in the northern hemisphere. With a similar incidence of ECMO use for 2009 influenza A(H1N1)–associated ARDS, rough estimates are that the United States and the European Union might expect to provide ECMO to approximately 800 and 1300 patients during the 2009-2010 winter, respectively.

Study Strengths and Limitations

Our study is the first to report, to our knowledge, the ECMO experience for 2009 influenza A(H1N1)–related ARDS using a population-based method in 2 developed countries, with well-established and nationally coordinated critical care systems. To our knowledge, this is the complete experience of ECMO in our region during winter. We report important aspects of the epidemiology, disease burden, and resource utilization for ECMO. We confirm previous findings of severe respiratory failure in a subset of patients with 2009 influenza A(H1N1),[3] and also demonstrate that most patients survived.

Our study has the inherent limitations of a case series. To improve accuracy, we used systematic methods of data collection, such as a case report form, trained research coordinators, predefined data field definitions, and a prospectively constructed data analysis plan. Although only 78% of patients tested positive for 2009 influenza A(H1N1), the remainder had confirmed influenza A during an outbreak in which the dominant strain of laboratory-confirmed influenza A has been 2009 influenza A(H1N1)[19] or had features of a preceding influenzalike illness complicated by pneumonia. In addition, their clinical characteristics were similar to those with confirmed 2009 influenza A(H1N1). As the diagnostic sensitivity of microbiological tests for 2009 influenza A(H1N1) is unknown, many of these patients are likely to have been infected with the virus.

We are unable to report on the possible outcome of our patients if ECMO had not been used, because allocation to receive ECMO was not conducted in the context of a randomized controlled trial. In our study, approximately 30% of patients who were mechanically ventilated with 2009 influenza A(H1N1) were treated with ECMO. This compares to an ECMO treatment rate for patients who were mechanically ventilated with 2009 influenza A(H1N1) of only 10% from all ICUs in 1 Australian state.[20] Of the 187 ICUs in Australia and New Zealand, only 15 provided ECMO services; however, these centers were often referred patients with severe respiratory failure despite advanced mechanical ventilatory support through semiformal referral networks.

Of the approximately 4950 patients requiring hospitalization for 2009 influenza A(H1N1) in Australia and New Zealand as of September 7, 2009 (4561 in Australia[21] and approximately 400 in New Zealand based on a similar proportion of confirmed cases[22]), the ICUs at the 15 ECMO centers received 252 patients, 68 of whom received ECMO. Of the 252 patients, 31 died, representing 17% of all 2009 influenza A(H1N1) deaths in Australia[21] and New Zealand.[22]

With the requirement to inform the northern hemisphere for the upcoming winter, we censored our data collection on September 7, 2009. Accordingly, final hospital outcomes were not available for some patients. However, death after weaning from ECMO or following ICU discharge was uncommon. In addition, we are unable to comment on the long-term outcome of our patients, particularly in relation to the degree of pulmonary dysfunction and quality of life. Finally, our estimates of ECMO use may be affected by changes in virulence of the virus or the development and deployment of an effective and safe vaccine.

CONCLUSION

In Australia and New Zealand, during the 2009 influenza A(H1N1) winter pandemic, there was a large increase in the use of ECMO for ARDS in patients compared with the winter of 2008. Despite their illness severity and the prolonged use of life support, most of these patients survived. This information should facilitate health care planning and clinical management for these complex patients during the ongoing pandemic.

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