ORIGINAL ARTICLE

Hong Kong's experience on the use of extracorporeal membrane oxygenation for the treatment of influenza A (H1N1)

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A video of extracorporeal membrane oxygenation is available at <www.hkmj.org>.

Objective To report Hong Kong's experience on the use of extracorporeal membrane oxygenation for the treatment of acute respiratory distress syndrome caused by influenza A (H1N1).

Design Multi-centred, retrospective observational study.

Setting Intensive care units in Hong Kong.

Patients Recipients of extracorporeal membrane oxygenation for confirmed influenza A (H1N1) infection from 1 May 2009 to 28 February 2010

Main outcome measure Hospital mortality.

Results During the study period, 120 patients were mechanically ventilated in intensive care units, among whom seven received veno-venous extracorporeal membrane oxygenation. The median (interquartile range) age of the latter patients was 42 (39-50) years, four had various chronic illnesses and one had a body mass index of greater than 30 kg/m^2. The median (interquartile range) time from symptom onset to hospital admission was 5 (4-7) days. Corresponding values for the duration of extracorporeal membrane oxygenation, mechanical ventilation, intensive care unit stay, and hospital stay were 6 (6-10), 19 (11-25), 19 (18-30), and 31 (25-55) days, respectively. One patient died (hospital mortality, 14%) and six made full recoveries. All seven patients received oseltamivir; in addition three received intravenous zanamivir, four received convalescent plasma, and one received hyperimmune immunoglobulin. Nosocomial infection was the commonest complication. There was no life- or limb-threatening complication directly attributable to extracorporeal membrane oxygenation.

Conclusion In response to the pandemic of influenza A (H1N1), some intensive care units in Hong Kong were able to offer extracorporeal membrane oxygenation to selected cases. In this small series, patient outcomes were similar to those reported in other observational studies, indicating that intensive care units in Hong Kong are capable of successfully introducing this technology. However, the cost-effectiveness and optimal delivery of this strategy remain uncertain.

Key words
Extracorporeal membrane oxygenation; Influenza A virus, H1N1 subtype; Intensive care units; Respiratory insufficiency

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Introduction

Since the Hong Kong Government escalated its response status for pandemic influenza A (H1N1) 2009 to Emergency Response Level on 1 May 2009, there were 120 intensive care admissions for influenza A (H1N1) deemed to require mechanical ventilation by the end of February 2010. Extracorporeal membrane oxygenation (ECMO) is a life-sustaining therapy, which has rarely been used for pulmonary disease in Hong Kong before 2009.[1] Since the preliminary results of the CESAR (Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure) trial[2] became available, interest in using ECMO for patients with reversible acute respiratory failure has re-emerged. Several observational reports of successful ECMO application in supporting patients with influenza A (H1N1) have been published,[3-12] with the Australian and New Zealand's experience[6] being particularly encouraging. A local case report on the use of ECMO for treating a critically ill influenza A (H1N1) patient, who finally succumbed, has

香港使用體外膜氧合治療甲型流感H1N1的經驗

目的 報告香港使用體外膜氧合（ECMO）治療因甲型流感H1N1引致的急性呼吸窘迫綜合症的經驗。

設計 多中心回顧性觀察研究。

安排 香港的深切治療病房。

患者 2009年5月1日至2010年2月28日期間，所有確診甲型流感（H1N1）及接受ECMO治療的病人。

主要結果測量 住院死亡率。

結果 研究期間共120位甲型流感（H1N1）患者在深切治療病房接受機械通氣，其中7人接受靜脈—靜脈ECMO治療。這7位病人的年齡中位數為42歲（四分位距IQR為39至50歲）；4人有慢性疾病，而1人的體重指數大於30 kg/m²。從病發到住院的時間中位數為5天（IQR4至7天），使用ECMO及機械通氣的時間分別為6天（6至10天）及19天（11至25天）。入住深切治療病房及住院時間分別為19天（18至30天）及31天（25至55天）。1名患者死亡（死亡率14%），其餘6人完全康復。所有患者均接受奧司他韋（oseltamivir）治療；其中3人額外接受扎那米偉（zanamivir）注射，4人接受療養血漿治療，1人接受高免免疫球蛋白治療。院內感染是最常見的併發症。並無發現直接由ECMO引致可威脅生命或肢體的併發症。

結論 在應對甲型流感（H1N1）大流行期間，香港一些深切治療病房提供ECMO治療給予個別患者。這些少量患者的住院死亡率跟外國一些觀察研究報告的結果相近，顯示香港的深切治療病房能夠成功引進此技術，可是它的成本效益和最佳的提供模式仍然不明確。

also been published.[13] The current observational series describes the Hong Kong's experience on using ECMO for the treatment of acute respiratory distress syndrome (ARDS) associated with influenza A (H1N1) during the first 10 months of the epidemic. A review of this experience may be helpful to guide future development of ECMO services in Hong Kong.

Methods

This report describes a multicentre, retrospective observational case series. All Hong Kong adult intensive care units (ICUs) with experience of using ECMO in the treatment of influenza A (H1N1) were invited to submit data. The authors were unaware of any paediatric cases involving ECMO for influenza A (H1N1) in Hong Kong during the study period. Relevant case notes of all intensive care patients admitted on or before 28 February 2010, with confirmed influenza A (H1N1) infection and who received ECMO, were reviewed. Demographic data, hospital survival, medical treatment received, data on relevant respiratory function and ventilatory support provided before, during and after ECMO treatment were retrieved. All documented complications, whether related or unrelated to ECMO, were also recorded.

Results

Between 1 May 2009 and 28 February 2010, there were 120 patients with influenza A (H1N1) who received mechanical ventilation in their respective Hong Kong ICUs. Seven (6%) of these patients received additional

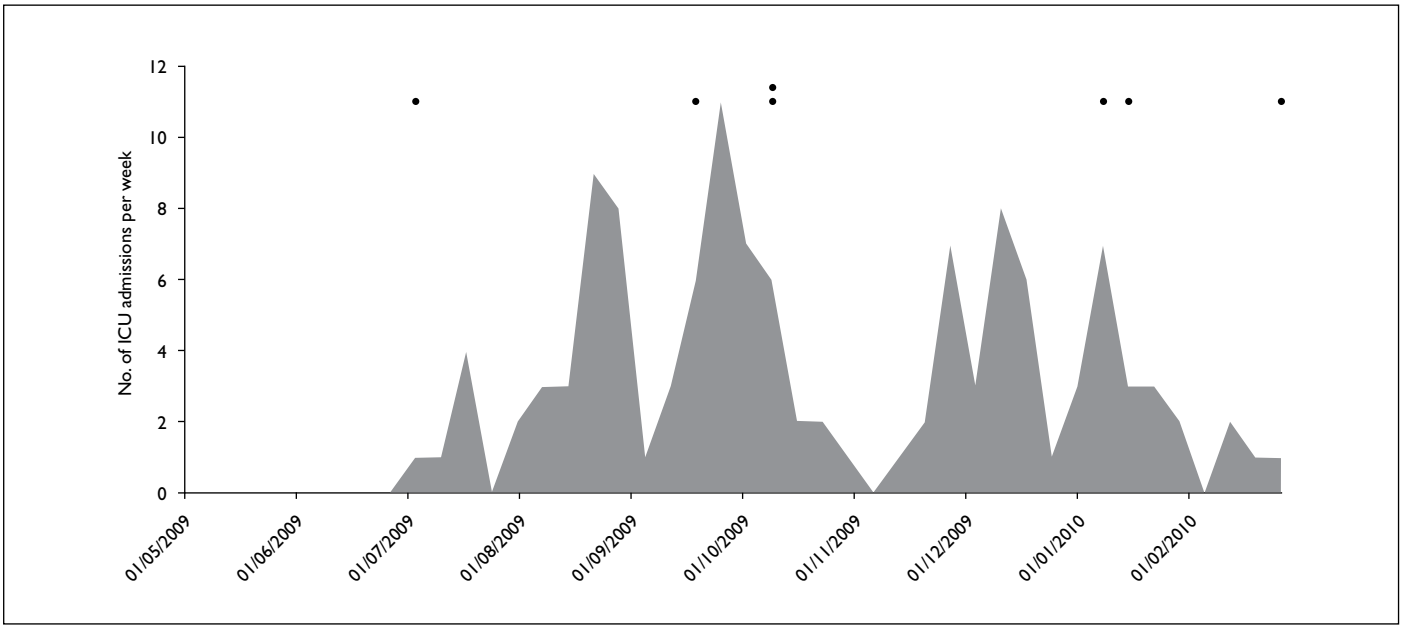

FIG 1. Epidemic curve of influenza A (H1N1) requiring intensive care unit (ICU) admission and receiving mechanical ventilation

• denotes case that required extracorporeal membrane oxygenation

TABLE 1. Characteristics of patients with influenza A (H1N1) requiring extracorporeal membrane oxygenation*

Characteristic†	Present study	Australia and New Zealand[6]	Canada[11]
No. of cases	7	61	6
Age (years)	42 (39-50) 44 ± 8	36 (27-45) –	- 22 ± 16
Male	2 (29%)	29 (48%)	1 (17%)
Body mass index (kg/m^2)	26 (26-27) 28 ± 4	29 (23-36) –	- 33 ± 7
Co-existing conditions			
Hypertension	2 (29%)	–	–
Diabetes	1 (14%)	9 (15%)	–
Chronic lung disease	1 (14%)	18 (30%)	–
Pregnancy or postpartum	0 (0%)	10 (16%)	–
Liver disease	2 (29%)	–	–
Duration (days)			
Symptom to hospital admission	5 (4-7)	5 (3-6)	6 (2-6)
Symptom to ICU admission	6 (4-7)	5 (3-7)	–
Hospital to ICU admission	0.1 (0.1-0.4)	–	0.5 (0-2.5)
Symptom to ECMO	11 (6-13)	8 (7-11)	–
ICU admission to ECMO	5 (1-7)	–	5 (3-8)
APACHE II score	17 ± 3	-	25 ± 3
Quadrant of radiograph infiltrates	4 (4-4)	4 (4-4)	-
Acute Lung Injury Score (Murray's score)	3.8 (3.8-3.9)	3.8 (3.5-4.0)	-
Before ECMO			
pH	7.30 (7.19-7.36) 7.26 ± 0.13	7.2 (7.1-7.3) -	- 7.31 ± 0.05
Pao_2/Fio_2 (mm Hg)	56 (53-71) 61 ± 11	56 (48-63) -	- 58 ± 17
Fio_2	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1 (1-1)
PEEP (cmH_2O)	16 (15-19) 14.9 ± 2.7	18 (15-20) -	- 20 ± 0
Peak inspiratory pressure (cmH_2O)	33 (30.5-35.5) 34.1 ± 4.9	36 (33-38) -	- 44 ± 42
Compliance (mL/cmH_2O)	22 (20-23)	-	-
$Paco_2$ (mm Hg)	55 (45-79)	69 (54-83)	-
Adjuncts for ventilation			
Prone ventilation	1 (14%)	12 (20%)	2(33%)
High-frequency oscillatory ventilation	0 (0%)	3 (5%)	3 (50%)
Nitric oxide	0 (0%)	20 (32%)	4 (67%)
Prostacyclin	0 (0%)	14 (22%)	-
Inotrope/vasopressor	5 (71%)	46 (68%)	2 (33%)
Renal replacement therapy	1 (14%)	16 (24%)	-
Cardiac arrest	0 (0%)	-	2 (33%)
Treatment of influenza A (H1N1)			
Oseltamivir	7 (100%)	64 (94%)	-
Intravenous zanamivir	3 (43%)	-	-
Convalescent plasma	3 (43%)	-	-
Hyperimmune immunoglobulin study	1 (14%)	-	-
Steroid	2 (29%)	-	-
Tracheostomy	1 (14%)	39 (57%)	-
Duration of mechanical ventilation (days)	19 (11-25)	25 (13-34)	26.5 (18-40.3)
Duration of ECMO (days)	6 (6-10)	10 (7-15)	15 (14-15)
ICU length of stay (days)	19 (18-30)	27 (16-37)	28 (19-38)
Hospital length of stay (days)	31 (25-55)	39 (23-47)	-
Hospital death	1 (14%)	14 (21%)	2 (33%)

* Data are shown as No. (%) of cases, median (interquartile range), or mean ± standard deviation

† ICU denotes intensive care unit, ECMO extracorporeal membrane oxygenation, APACHE Acute Physiology and Chronic Health Evaluation, Pao_2/Fio_2 partial pressure of oxygen/fraction of inspired oxygen, PEEP positive end-expiratory pressure, and $Paco_2$ partial pressure of carbon dioxide, arterial

TABLE 2. Characteristics of individual patients with influenza A (H1N1) requiring extracorporeal membrane oxygenation*

Case No.	Sex/age (years)	BMI (kg/m²)	Co-morbidity	Outcome	Muscle relaxant infusion	Hospital admission to ECMO (days)	ECMO/MV/ ICU/hospital stay (days)
1	F/37	26	Nil	Died	Yes	6	13/19/19/19
2	F/42	28	Chronic active hepatitis	Home	No	5	6/21/28/31
3	F/47	27	Asthma hypertension	Home	Yes	17	29/48/49/68
4	M/54	26	Diabetes hypertension	Home	Yes	1	6/10/19/52
5	M/41	25	Hepatitis B carrier	Home	No	1	6/13/17/21
6	F/53	35	Nil	Home	No	7	5/31/32/58
7	F/34	24	Nil	Home	No	1	6/9/15/29

* BMI denotes body mass index, ECMO extracorporeal membrane oxygenation, MV mechanical ventilation, ICU intensive care unit, and MRSA methicillin-resistant *Staphylococcus aureus*

ECMO in three ICUs. The case admission trends and timing of the ECMO cases are shown in Figure 1. All influenza A (H1N1) infections were confirmed by real-time polymerase chain reactions. No patients with severe pneumonia due to any other aetiology received ECMO during this period. The characteristics of these seven patients are summarised in Table 1, alongside data from other countries. Further details of the patients are shown in Table 2. One previously reported patient died in the ICU from multiple organ failure,[13] whilst the remaining six were discharged home having fully recovered. Thus the crude hospital mortality rate was 14%.

All seven patients received veno-venous ECMO (VV-ECMO). The median treatment duration (interquartile range [IQR]) was 6 (6-10) days. Femoral drainage cannulae of either 21 Fr or 23 Fr were used in all the patients, none of whom were deemed to require dual drainage cannulae for ECMO support (high-flow VV-ECMO). Centrifugal pumps were used in all cases. Either the femoral or jugular vein was used for placing the return cannula. Femoral return cannulae used were of 18 Fr to 21 Fr, while jugular cannulae were 15 Fr to 17 Fr. Unfractionated heparin was infused for systemic anticoagulation, with a target activated partial thromboplastin time of 60 seconds. A total of 13 oxygenators—five non–heparin-coated (Capiox SX, Terumo, Japan) and eight heparin-coated (Quadrox-PLS, Maquet, Germany)—were used. All five non–heparin-coated oxygenators were used in one patient to provide 16 days (3+3+3+4+3 days) of treatment. The last treatment (3 days) for that patient was provided using a heparin-coated oxygenator. A total of seven heparin-coated oxygenators were used for providing treatment to the remaining six patients. Five patients were treated with only one oxygenator, while one patient was treated with two. The median (IQR) service life of the heparin-coated oxygenator was 7 (6-13) days. No significant clotting of the heparin-coated oxygenator necessitated its change.

A total of 49 units of packed cells were transfused during the total ECMO duration of 70 days, resulting in a mean of 0.7 units being used per treatment day. None of the patients had significant bleeding, for which surgical intervention or endoscopy was deemed necessary. Significant haemolysis was noted in two patients, and minor haemorrhage from the cannulation site in two. No patient suffered macroscopic limb ischaemia or other life-threatening complications (circuit dislodgement,

Treatment for influenza A (H1N1) [daily dose x days]	Infection	During ICU stay	After ICU discharge
Oseltamivir Nebulised zanamivir (60 mg x 2) N-acetylcysteine (1.2 g x 19) Zinc (100 mg x 2)	-	Haemolysis Pneumothorax	Not applicable
Oseltamivir Nebulised zanamivir (60 mg x 12) Hydrocortisone (200 mg x 9) Convalescent plasma (500 mL x 1) N-acetylcysteine (3.6 g x 2) Zinc (100 mg x 2) Selenium (55 µg x 2)	-	Delirium	Nil
Oseltamivir Intravenous zanamivir	Candidaemia MRSA bacteraemia	Haemolysis Delirium	Nil
Oseltamivir Nebulised zanamivir (60 mg x 3) Intravenous zanamivir Methylprednisolone (120 mg x 3, then tapered off in 4 days)	*Stenotrophomonas* pneumonia	Critical illness polyneuropathy	Pulmonary embolism
Oseltamivir Convalescent plasma (500 mL x1)	*Klebsiella* pneumonia *Escherichia coli* urinary tract infection Pseudomembranous colitis	Nil	Nil
Oseltamivir Intravenous zanamivir Convalescent plasma (500 mL x 1)	*E coli* urinary tract infection	Minor cannulation site bleeding	Nil
Oseltamivir Hyperimmune immunoglobulin study	MRSA pneumonia	Delirium Minor cannulation site bleeding	Transient vocal cord palsy

circuit blockage, equipment failure, air embolism, or massive pulmonary embolism) directly attributable to ECMO.

A summary of patients' respiratory parameters before and after ECMO is shown in Figure 2. The median partial pressure of oxygen/fraction of inspired oxygen (Pao_2/Fio_2) [IQR] improved from 56 (53-71) mm Hg to 183 (154-222) mm Hg with the initiation of ECMO (Wilcoxon signed rank test, P=0.018). The initial blood flow and oxygen flow for the ECMO ranged from 2.5 L/min to 5.7 L/min and 3 L/min to 7 L/min, respectively.

None of the patients received any inotrope or vasopressor before ICU admission, but five patients received noradrenaline infusions (dosages ranging from 5.3 to 10.6 µg/min) before the institution of ECMO. All the patients received an inotrope or vasopressor at sometime during ECMO support. The maximum dosage of noradrenaline administered to any of the surviving patients was 20 µg/min; all the patients were weaned off noradrenaline infusions before termination of ECMO.

Patient 3 developed acute kidney injury, for which continuous renal replacement therapy (CRRT) was instituted before ECMO. Patients 1, 4, 5, and 6 received CRRT during ECMO support. Patient 1 died while on CRRT. Only patient 4 received short-term renal replacement therapy after cessation of ECMO; after recovery, he achieved acceptable renal function, with a plasma creatinine level of 96 µmol/L when discharged from hospital.

Medical therapy for the influenza A (H1N1) infection was determined by individual physicians in-charge. All patients received oseltamivir at dosages of 75 mg (dose adjusted for renal impairment) to 600 mg per day, according to body weight and the individual physician's preference. The median (IQR) treatment duration was 17 (14-17) days. Three patients received additional intravenous zanamivir for 5 to 7 days. The loading dose was 600 mg, and the maintenance dose was adjusted according to renal function. Three patients received 500 mL of convalescent plasma intravenously. Other individualised treatments included nebulised zanamivir, intravenous steroids, N-acetylcysteine, zinc, and selenium (Table 2). One patient was enrolled into a randomised control trial of hyperimmune immunoglobulin,[14] and had a 50% chance of receiving generic immunoglobulin or immunoglobulin harvested form subjects with high influenza A (H1N1) virus neutralising antibody titres.

The median (IQR) duration of mechanical ventilation was 19 (11-25) days. Patient 4 received

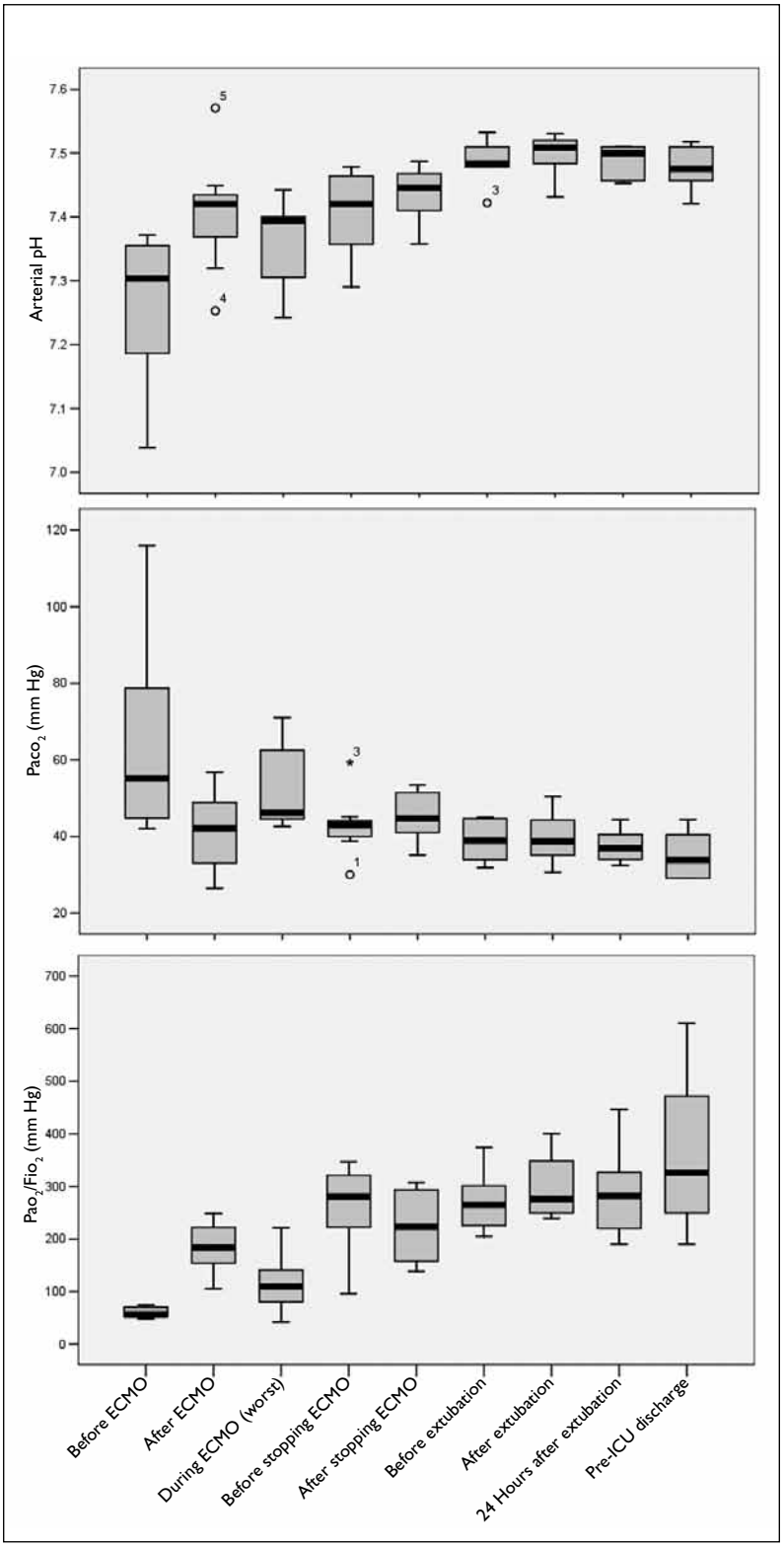

FIG 2. Respiratory parameters of patients with influenza A (H1N1) receiving ECMO
ECMO denotes extracorporeal membrane oxygenation, and ICU intensive care unit; numbers in superscript indicate the case number of the outlying values

a day of non-invasive ventilation after extubation. An obese patient (No. 6) underwent tracheostomy for weaning, de-cannulation of the tracheostomy was carried out before discharge from the ICU. The median (IQR) ICU length of stay was 19 (18-30) days, and the median (IQR) hospital length of stay was 31 (25-55) days. Time from hospital admission to ECMO correlated significantly with the length of ICU stay (Spearman's rho=0.929, P=0.0025), but not the length of hospital stay (Spearman's rho=0.464, P=0.29).

Three patients developed delirium during their ICU stay. The relationship with ECMO to delirium was unclear as the cause could have been related to the use of oseltamivir,[15] sedatives, the critical illness itself, or an encephalitis caused by the influenza virus. In no case was cerebrospinal fluid obtained. In patient 7, who had an episode of delirium and a transient vocal cord palsy after extubation, the brain magnetic resonance image revealed no abnormality. She had recovered fully when discharged from hospital.

Nosocomial sepsis occurred in five (71%) patients. Two (29%) had *Escherichia coli* urinary tract infections, two (29%) had nosocomial methicillin-resistant *Staphylococcus aureus* infections (one had bacteraemia and one pneumonia), and one (14%) had *Candida* cultured from the blood. All nosocomial infections resolved after antimicrobial therapy.

Patient 4 had persistent bilateral ankle oedema. His X-ray chest after ICU discharge revealed cardiomegaly; echocardiography showed significant tricuspid regurgitation and a dilated right ventricle (5.5 cm). Contrast-enhanced computed tomography of the chest revealed a small filling defect in the anterior basal segmental artery territory of the right lower lobe, suggestive of pulmonary embolism. His pulmonary embolism severity index was 64, which is considered Class I (or very low risk).[16] He received systemic anticoagulation and had an uncomplicated course.

Discussion

Of the seven patients with severe ARDS and influenza A (H1N1) treated with ECMO, six survived to hospital discharge, and there were no directly attributable severe complications associated with the use of ECMO. All the patients in this series satisfied the entry criteria for ECMO reported in the CESAR trial.[2] Their Acute Lung Injury score and the Pao_2/Fio_2 ratios before ECMO were similar to those in other reported series.[6,11] The rate of ECMO use in all mechanically ventilated patients with influenza A (H1N1) was 6% (7/120), which was similar to the 4% (6/168) reported in a Canadian series,[11] and 9% (68/722) in Australasian series.[6,17] Similarly, the observed hospital mortality (14%) compared favourably with Australasian[6] and Canadian[11] experience. However, this could be the result of selection biases. First, co-morbidity of our patients was relatively minor, whilst approximately 30% of patients in the Australasian series had chronic

lung disease,[6] and two (33%) in the Canadian series[11] had experienced a cardiac arrest before ECMO. Also, none of the patients in our series had known concomitant bacterial pneumonia on presentation, in which case the mortality rate could reach 50%.[5] While three (43%) patients in our series received convalescent plasma, it is unknown whether these unproven therapies had any effect on the outcomes.

A limitation of our series was the small number of patients. As ECMO was practised in some, but not other, ICUs, a matched case-control study had been considered to further evaluate any potential benefits (or harm) from ECMO treatment of influenza A (H1N1). However, the estimated power of such a study would only be 49%, assuming there were 21 matching control subjects (in 1:3 ratio) with a hospital mortality of 49% (estimated using data from the CESAR trial[2]).

In response to the influenza A (H1N1) pandemic, some ICUs in Hong Kong provided ECMO, which they had not provided previously. In establishing a new service, a traditional approach is to learn from a 'centre of excellence' and follow generally agreed 'best practice' (Best Practice Model). Using such a model, the optimal way of establishing an ECMO service would be: first to ensure hands-on training at that centre, and second to start ECMO therapy elsewhere under the direct supervision of experienced trainers. Services of ECMO established using this model could be of reasonable quality, but establishing such a process could be challenging. Also, this model per se does not guarantee continuous quality improvement and adaptation to changes in internal and/or external factors.

For a rapid response to a possible pandemic, an ECMO service was introduced in some ICUs. Introduction of such new technology can be assessed using concepts from the Capability Maturity Model,[18,19] which is a generic model for establishment and continual improvement of services or products. In this model, the capability and maturity of a process or service could be divided into five levels (Table 3). Level 1 corresponds to initial success, relying on competence of the staff, and appears to have been achieved for ECMO in some Hong Kong ICUs. Given the diminishing pressure from the pandemic, the relatively easy availability of training and expert advice from overseas centres of excellence, the Best Practice Model guidelines seem to be an attractive option to advance a mature ECMO capability in local ICUs. However, as its cost-effectiveness remains unclear, it is debatable whether it is necessary to establish a permanent ECMO capability in Hong Kong, and what form it should take.

The number of ECMO patients in this series was insufficient to allow meaningful risk assessments, however life- or limb-threatening complications were not observed. The exclusive use of VV-ECMO, the high-quality surgical support, or the well-established experience with veno-venous circuits for renal replacement therapy in the involved ICUs may have contributed to this lack of complications. By comparison, only 93% of patients in the Australasian series[6] and 66% in the Canadian series[11] received VV-ECMO. Without the requirement for an arterial cannula, the chances of bleeding from the cannulation site, limb ischaemia, embolism to the extremities or the brain were minimised. With VV-ECMO, blood flow to the lungs is maintained, which theoretically minimises the risk of pulmonary ischaemia and the pulsatile nature of arterial flow is maintained and could be of benefit to various organs.[20] Lastly, the preferential use of a heparin-coated circuit and oxygenator reduced the need for systemic anticoagulation, and hence the bleeding risk.

TABLE 3. General description of the various levels in the Capability Maturity Model

Level	Description
1 – Initial	Works are performed on an 'ad hoc' basis and processes are in a state of dynamic change. Success depends on the competence and heroics of the people.
2 – Repeatable	Processes become repeatable, and possibly with consistent results. Repeatability depends on staff experience, rather than documentation. Process discipline (division of labour) exists but is unlikely to be rigorous.
3 – Defined	Processes are formally defined and documented. These standard processes are understood by the staff and are followed, such that repeatability can be expected. Some degree of improvement in the processes may occur over time.
4 – Managed	Both the quality of processes and the quality of end-products are quantitatively measured and controlled. Processes are added or adjusted without any measurable losses of quality or deviations from specifications.
5 – Optimising	The focus is continual improvement and preventing defects by proactively addressing the strengths/weaknesses of the processes and successfully exploiting innovations in technology. Quantitative process improvement objectives are established.

Conclusion

Since the onset of pandemic of influenza A (H1N1) in Hong Kong in 2009, some ICUs have provided ECMO for selected patients. Up to 28 February 2010, seven patients with confirmed severe influenza A (H1N1) infection received ECMO. One of them succumbed while six made a full recovery. In this small series, patient outcomes were similar to those reported in other observational studies, and no directly attributable life-threatening complications were observed, suggesting that local ICUs are capable of successfully introducing the technology. However, the cost-effectiveness and optimal delivery of this strategy remains uncertain.

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References

1. Sihoe AD, Ng VM, Liu RW, Cheng LC. Pulmonary alveolar proteinosis in extremis: the case for aggressive whole lung lavage with extracorporeal membrane oxygenation support. Heart Lung Circ 2008;17:69-72.
2. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351-63.
3. Torres JP, O'Ryan M, Herve B, et al. Impact of the novel influenza A (H1N1) during the 2009 autumn-winter season in a large hospital setting in Santiago, Chile. Clin Infect Dis 2010;50:860-8.
4. Parcevaux M, Antok E, Boisson V, Grabel C, Bugnon O, Winer A. Acute respiratory distress due to Influenza A (H1N1) S-OIV and extracorporeal oxygenation: the benefit of a multidisciplinary care network [in French]. Ann Fr Anesth Reanim 2010;29:145-8.
5. Buckley E, Sidebotham D, McGeorge A, Roberts S, Allen SJ, Beca J. Extracorporeal membrane oxygenation for cardiorespiratory failure in four patients with pandemic H1N1 2009 influenza virus and secondary bacterial infection. Br J Anaesth 2010;104:326-9.
6. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, Bailey M, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA 2009;302:1888-95.
7. Flagg A, Danziger-Isakov L, Foster C, et al. Novel 2009 H1N1 influenza virus infection requiring extracorporeal membrane oxygenation in a pediatric heart transplant recipient. J Heart Lung Transplant 2010;29:582-4.
8. Grasselli G, Foti G, Patroniti N, et al. A case of ARDS associated with influenza A - H1N1 infection treated with extracorporeal respiratory support. Minerva Anestesiol 2009;75:741-5.
9. Kao TM, Wang CH, Chen YC, Ko WJ, Chang SC. The first case of severe novel H1N1 influenza successfully rescued by extracorporeal membrane oxygenation in Taiwan. J Formos Med Assoc 2009;108:894-8.
10. Weber SA, Ostermann A, Pohl C. Fulminant, life-threatening influenza A/H1N1 virus infection [in German]. Dtsch Med Wochenschr 2009;134:2447-50.
11. Freed DH, Henzler D, White CW, et al. Extracorporeal lung support for patients who had severe respiratory failure secondary to influenza A (H1N1) 2009 infection in Canada. Can J Anaesth 2010;57:240-7.
12. Sigurdsson GH, Möller AD, Kristinsson B, et al. Intensive care patients with influenza A (H1N1) infection in Iceland 2009 [in Icelandic]. Laeknabladid 2010;96:83-90.
13. Liong T, Lee KL, Poon YS, et al. The first novel influenza A (H1N1) fatality despite antiviral treatment and extracorporeal membrane oxygenation in Hong Kong. Hong Kong Med J 2009;15:381-4.
14. Use of hyperimmune intravenous immunoglobulin to treat serious human swine influenza infections. University of Hong Kong website: http://web3.hku.hk/facmed/hkumed/doc_download.php?id=33&post_date=26 Aug 092009. Accessed 30 Mar 2010.
15. Nakamura K, Schwartz BS, Lindegårdh N, Keh C, Guglielmo BJ. Possible neuropsychiatric reaction to high-dose oseltamivir during acute 2009 H1N1 influenza A infection. Clin Infect Dis 2010;50:e47-9.
16. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172:1041-6.
17. ANZIC Influenza Investigators, Webb SA, Pettilä V, Seppelt I, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009;361:1925-34.
18. Chrissis MB, Konrad M, Shrum S. CMMI: guidelines for process integration and product improvement. 2nd ed. Upper Saddle River, NJ: Addison-Wesley; 2007.
19. Forrester EC, Buteau BL, Shrum S. CMMI for services: guidelines for superior service. Upper Saddle River, NJ: Addison-Wesley; 2010.
20. Ji B, Undar A. An evaluation of the benefits of pulsatile versus nonpulsatile perfusion during cardiopulmonary bypass procedures in pediatric and adult cardiac patients. ASAIO J 2006;52:357-61.